Contents

Proceedings of the International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle Lima, Peru, May 30–June 1, 2001

Rainer Gross, Archana Dwivedi, Noel W. Solomons, guest editors

---

Food and Nutrition Bulletin, vol. 24, no. 3 (supplement)

United Nations University Press
Published by the International Nutrition Foundation for The United Nations University
53-70 Jingumae 5-chome, Shibuya-ku, Tokyo 150-8925, Japan
Tel.: (03) 3499-2811 Fax: (03) 3406-7345
E-mail: mbox@hq.unu.edu
ISSN 0379-5721
Design and production by Digital Design Group, Newton, MA USA
Printed on acid-free paper by Webcom Ltd., Toronto, ON Canada

Introduction to the Proceedings of the International Research on Infant Supplementation (IRIS) Initiative

Rainer Gross, Archana Dwivedi, and Noel W. Solomons, Guest Editors

Abstract

In 2001, students and professionals from 13 nations were hosted by UNICEF for the International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle in Lima, Peru, May 30–June 1, 2001. Workshop participants engaged in both narrow and broad discussions of ways to combat multiple micronutrient deficiencies in developing countries. Preliminary data from four common-protocol studies conducted in Peru, South Africa, Indonesia, and Vietnam were presented. Participants also discussed the immediate, preliminary, and interim issues that could guide both policy and planning of future studies of multiple micronutrient deficiency. Among the studies highlighted was the International Research on Infant Supplementation (IRIS) I trial. A review of IRIS I yielded some confirmation of the efficacy using a crushable "foodlet" (i.e., cross between food and tablet) as a supplementation vehicle, as well as concerns about potential adverse consequences of nutrient-nutrient and nutrient-nutriture interactions. Other plenary topics illustrated the practical matters of how the IRIS I logistics and operations were built, and several focused on how to best design follow-up research on infant supplementation. Finally, a series of working groups allowed for in-depth discussions on the topics of community and policy, monitoring and implementation, and research. Researchers continue to try to identify efficient and effective programs suited to the low-income settings in which infant multimicronutrient malnutrition occurs. The papers in these proceedings elaborate on several aspects of the IRIS study, and they are published in the hope that their analysis by readers will produce wider dissemination of the details of this devastating problem.

Rainer Gross and Archana Dwivedi are affiliated with UNICEF, New York City, USA. Noel W. Solomons is affiliated with the Center for Studies of Sensory Impairment, Aging and Metabolism (CeSSIAM) in Guatemala City, Guatemala. Address for correspondence: Rainer Gross, Chief, Nutrition Section, Programme Division, UNICEF, 3 UN Plaza, New York, NY 10017; email: rgross@unicef.org.

Key words: infant supplementation, IRIS, minerals, multiple micronutrients, UNICEF, vitamins

Introduction: the worldwide context of multiple micronutrient deficiencies

Since the early 1990s, an intense resurgence of academic and public health interest in the epidemiology and biology of vitamin and mineral deficiencies has occurred around the world. Adequate intake of micronutrients is necessary for growth, physical and motor development, resistance to acute disease, and general well being. Surveys and intervention trials show that certain subgroups of low-income societies, such as infants, toddlers, adolescent girls, and pregnant and lactating women, suffer developmental and/or nutrition consequences of inadequate intakes and uptakes of iron, vitamin A, iodine, zinc, riboflavin, selenium, and vitamin B_{12}. Targeted supplementation has been shown to be an appropriate remedy for such deficiencies. However, the use of single-nutrient interventions, along with the failure of many programs to produce sustainable and effective long-term results, have left some public health and nutrition professionals questioning the effectiveness of single-nutrient interventions, as opposed to integrated strategies that simultaneously address multiple micronutrient deficiencies. [1]

The steps leading to IRIS

The centerpiece of the discussions in Peru was the presentation of preliminary descriptive data from IRIS I, which, in late 2000, studied 6- to 12-month-old infants from low-income families in Peru, South Africa, Indonesia and Vietnam. The IRIS project was the result of a crescendo of voluntary meetings among professionals interested in multiple micronutrient deficiencies beginning in Singapore in 1998, and continuing through stops in New York in 1999 and Rio de Janeiro in 1999

[1]. The meeting in Rio de Janeiro identified three key theoretical convictions: (1) Micronutrient deficiencies rarely occur as single-nutrient problems, but rather as deficiencies of multiple micronutrients concurrently and, therefore, should be addressed concurrently; (2) The combination of micronutrients to provide an average of one recommended dietary allowance (RDA) or less is inherently safe; and (3) A convenient, novel, and perhaps intrinsically sustainable approach to public health delivery of multiple micronutrients to an infant population would be in the form of an edible food substance. The term "foodlet" was coined within one of the working groups at the Rio de Janeiro meeting [1].

The momentum from the Brazil meeting led directly to a four-nation, multicenter, collaborative field intervention trial with a consortium of investigators under the IRIS banner. Not to become complacent, the conveners were already discussing a follow-up process exploring alternative forms of edible vehicles for infant supplementation in a fourth meeting held in Cape Town in late 2000. Finally, once data had been collected and collated from IRIS I, it was time to convene a collective consideration of the findings. Lima, Peru in May 2001 was the venue for this international workshop to review IRIS I and its implications for the state of the art of multiple micronutrient supplementation.

Context of the Lima meeting

The contributions in this supplement attest to the rich and diverse set of considerations that emerged in the Lima workshop. A wide range of institutions and professionals were represented, including local and international pharmaceutical companies, government agencies, bi-national and multinational agencies, policy institutions, and universities. Lima not only provided the backdrop of a nation with pockets of extreme poverty and a tumultuous political panorama, but was also one of the study sites of IRIS I. The continents in which the parallel IRIS projects were conducted—Africa, Asia, and South America—were represented at the workshop, as were North and Central America and Europe.

Workshop participants included a wide range of professionals, including young students and scientists for whom IRIS I was their first professional endeavor, mid-career professionals with a track record in micronutrient issues, and distinguished leaders in the field of nutrition. Participants were particularly fortunate to hear a discussion on iodine interventions by Dr. Eduardo Pimentel, Minister of Health for the Republic of Peru and one of the world's most renowned experts on iodine-deficiency disorder. In addition, several workshop sessions were chaired by renowned researcher and professor Dr. Nevin Scrimshaw. Perhaps the meeting was most favored, however, by the diverse combination of attendees, who included both skeptics and advocates of combining multiple micronutrients into common intervention strategies.

Highlights and conclusions from the workshop

The issue of dosage (one RDA for infants) was a central theme of the workshop [1]. In 2001, the United States and Canada released the final versions of their reports on *Dietary Reference Intakes* (DRI), which included adequate intakes (AI) and tolerable upper limits (UL) [2]. The lessons learned from the DRI process have been skillfully teased out by Bienz et al. [3] in relation to appropriate combinations of micronutrients for infants and toddlers. But North America is not the geographic stage for the endemicity of micronutrient malnutrition, begging the question as to whether the North American DRIs or the United Nations agencies' (World Health Organization, WHO; Food and Agriculture Organization, FAO) norms are applicable in terms of reference for developing societies.

Technical considerations, both theoretical and practical, regarding the supplementation vehicle used in IRIS I were also discussed at the workshop. The crushable, edible tablet, or "foodlet," was manufactured for all four IRIS sites by a pharmaceutical company in Lima, with technical oversight by Roche affiliates around the world [4]. The food technology and pharmaceutical processes of the foodlet's pretesting, manufacture, packaging, and distribution set the stage for both the logistics and the efficacy considerations of the multicenter trial.

Kamp et al., in these proceedings [5], discuss the topic of bioavailability of the nutrients contained in the foodlet. Before IRIS I began, a bioavailability study of healthy adults confirmed that the foodlet's micronutrients were reasonably absorbable on an empty stomach in the presence of excipient agents and compounding technology in the foodlet vehicles. Although a study of adults is not totally predictive of the bioavailability the same formula would have in infants, it represented the most practical population in which to test the vehicle.

The same paper by Kamp et al. compares the ingestion of the supplement on an empty stomach and in the presence of a cornstarch porridge. This model turned out later to be providential, as the planned "empty stomach" delivery of the common-protocol design was not possible in South Africa. At that site, local circumstances would force the foodlet's dose of micronutrients to be given mixed into the local maize porridge weaning food of rural KwaZulu-Natal; hence, all of the groundwork on micronutrient bioavailability turns out to be relevant to a comprehensive interpretation of the data from the field.

At the time of this writing, the descriptive data on the baseline state of the respective populations and the comparative analysis of responses to interventions in the four sites have yet to be published. What Smuts and coworkers [6] from all around the field and laboratory settings of IRIS I have prepared for the reader here is a carefully detailed explanation of all of the common procedures and quality-control features of the multicenter protocol. In addition, the caveats of individual differentiation in application of the protocol in the given sites are discussed. The most important caveats were less intense surveillance and the mixing of the foodlet into a complementary food among the infants in South Africa.

Preliminary findings from IRIS I were offered at the workshop in Lima. The age distribution of infants enrolled among the centers was firmly comparable; not surprisingly, the weights-for-age of children in coastal Peru and rural South Africa were much greater than those of children in the two Southeast Asian sites. Of particular note was an apparent difference in growth experience in the children who received one additional RDA of iron daily compared with those who did not have daily iron (either by randomization to placebo tablets or to weekly rather than daily iron). Those with more regular supplementary iron exposure showed a trend toward slower growth through the 6-month interval. Given other experiences in which multiple micronutrients have a paradoxical effect of more adversity compared with single nutrients [7] and the growing instances in which iron given to those with existing iron stores had adverse consequences [8], some researchers advocate caution with regard to using dosage of one RDA, saying that the dosages may not be as innocuous as they sound.

The immediate relevance of the Lima workshop was that it left participants looking toward the future for another multicenter trial. Because an additional 6-month follow-up of subjects was conducted in the Peruvian sample (IRIS II), the enumeration for the plan to repeat formal 6-month intervention trials in the original four sites has been dubbed IRIS III [9]. The notion is to adopt another little food vehicle—this time not the "foodLET" (tablet) model [4, 5] but rather the "FOODlet" (fat-based spread) approach. In a paper in these proceedings, Briend and Solomons discuss the development of such a vehicle [10]. Lessons learned in IRIS I are sure to bear on the design and safety considerations for the next round of research.

In the working group on research [11], both technical and philosophic points were emphasized. We (Gross and Solomons), in a paper in these proceedings, present an expanded treatise on that theme, emphasizing that a research design must be crafted and executed with a maximal level of quality [12]. It advances neither science nor any resulting programmatic or policy decisions if experiments are flawed. That resources were limited in the IRIS trial and are generally scarce in any developing country is clear. However, the principles of quality control in field research trials are well understood and re-enforcing them among our colleagues is part of the importance of our review. Given the power disequilibrium between those who conceive and finance research in developing countries and those who are the subjects of study, research efforts can never be divorced from ethical principles [13]. The ethical rules underlying the respect for the autonomy of participating subjects (respecting free will, without coercion) as well as the principles of non-malificence (first do no harm), beneficence (try to do good for society), and justice (non-discrimination, greatest good for the greatest number, compensatory effort for those on the margin) must always be considered when designing interventions.

There was also a working group on community and policy, which was charged with examining the applied aspects of any eventual implementation of multiple micronutrient supplementation to infants at the public health level [14]. Originally, the organizers had planned to have two working groups: one for the community levels and another for the national and international levels. For practical reasons, these two topics were combined, making evident the level of complexity and interconnectedness of stakeholders' considerations, from international agencies to the rural village or urban neighborhood level. Any eventual application of this new modality to bring multiple micronutrients to infants and children requires both logistical and behavioral aspects in its implementation and systematic monitoring of the process and impact [15]. The extent of its efficacy and concerns about safety prompted considerations of monitoring not only biochemical indicators of vitamin and mineral status, but functional consequences (such as growth) as well.

In order to include all papers presented at the Lima workshop, we have reprinted three papers previously published in the *Food and Nutrition Bulletin* (Vol. 23, No. 3, pp. 309–316) under the heading "International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle, Lima, Peru, May 30–June 1, 2001."

Invitation to *Food and Nutrition Bulletin* readers

The editors of the *Food and Nutrition Bulletin* have provided a valuable opportunity for a forum on appropriate interventions to combat multi-micronutrient deficiencies in infants, including issues of safety and efficacy. This supplement to the *Bulletin* presents the major plenary discussions and workshop reports from the meeting in Lima. Our invitation as you read these proceedings is to join with us in developing your own considerations and best judgments from the contri-

butions that follow. Only with a wide awareness and shared wisdom from nutrition and food science professionals around the world will the malnourished infants in low-income settings become the ultimate beneficiaries of the efforts of ongoing research translated into sound policy and workable and sustainable programs.

References

1. Gross R. Micronutrient supplementation throughout the life cycle. New York: UNICEF, 2001.
2. Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy of Sciences, 2001.
3. Bienz D, Cori H, Hornig D. Adequate dosing of micronutrients for different age groups in the life cycle. Food Nutr Bull 2003;24:S7–S15.
4. Lock G. The foodLET vehicle designed for and used in the IRIS I intervention. Food Nutr Bull 2003;24: S16–S19.
5. Kamp F, Jandel D, Hoenicke I, Pietrzk K, Gross R, Trugo NMF, Donangelo CM. Bioavailability of iron, zinc, folate, and vitamin C in the IRIS multi-micronutrient supplement: Effect of combination with a milk-based cornstarch porridge. Food Nutr Bull 2003; 24:S20–S26.
6. Smuts CM, Benadé AJ, Berger J, Hop LT, Lopez de Romaña G, Untoro J, Karyadi E, Erhardt J, Gross R. IRIS I: A foodlet-based multiple-micronutrient intervention in 6- to 12-month-old infants at high risk of micronutrient malnutrition in four contrasting populations: Description of a multicenter trial. Food Nutr Bull 2003; 24:S27–S33.
7. Ologoudou K, Ramakrishnan U, Neufeld L, Gonzalez-Cossio T, Rivera J. Effect of multivitamin mineral supplements on infant iron status: a controlled trial in Mexico. FASEB J 2003;17:A1101.
8. Idjradinata P, Watkins W, Pollitt E. Adverse effect of iron supplementation on weight gain of iron-replete young children. Lancet 1994;343:1252–4.
9. Lopez de Romaña G, Gross R. IRIS III: proposal of a multicenter efficacy study using a high-energy, micronutrient-dense spread. Food Nutr Bull 2003; 24: S39–S41.
10. Briend A, Solomons NW. The evolving applications of spreads as a FOODlet for improving the diets of infants and young children. Food Nutr Bull 2003; 24:S34–S38.
11. Berger J, Solomons NW (Rapporteurs). Report of the research needs working group. In: Gross R, Dwivedi A, Scrimshaw N, eds. International workshop on multi-micronutrient deficiency control in the life cycle, Lima, Peru, May 30–June 1, 2001. Food Nutr Bull 2002;23:313–6.
12. Gross R, Solomons NW. Multiple micronutrient deficiencies: future research needs. Food Nutr Bull 2003;24:S42–S53.
13. Caballero B. Ethical issues for collaborative research in developing countries. Am J Clin Nutr 2002;76:717–20.
14. Boy E, Scrimshaw N (Rapporteurs). Report of the community and policy working group. In: Gross R, Dwivedi A, Scrimshaw N, eds. International workshop on multi-micronutrient deficiency control in the life cycle, Lima, Peru, May 30–June 1, 2001. Food Nutr Bull 2002;23: 310–1.
15. Finley D, Schümann K, Hess-Beinz D. (Rapporteurs). Monitoring and impact evaluation of a multi-micronutrient supplementation program. In: Gross R, Dwivedi A, Scrimshaw N, eds. International workshop on multi-micronutrient deficiency control in the life cycle, Lima, Peru, May 30–June 1, 2001. Food Nutr Bull 2002;23: 312–3.

Adequate dosing of micronutrients for different age groups in the life cycle

Denise Bienz, Hector Cori, and Dietrich Hornig

Editors' Note

The Infant Research on Infant Supplementation (IRIS) protocol came out of the workshop in this series held in 1999 in Rio de Janeiro, Brazil. The concept was to provide interventions with either daily micronutrients as a single RDA dosage or weekly micronutrients as a two-fold multiple of the RDA. At the time, the only complete sets of daily intake recommendations based on human vitamin and mineral requirements dated to 1988 (WHO/FAO) and 1989 (10th Edition of the Recommended Dietary Allowances). The authors of this paper have made an exhaustive review and update of the emerging recommendations for nutrient intake throughout the life cycle coming out of the Dietary Reference Intakes deliberations in North America. These also introduced a systematic approach to recommending upper tolerable limits for regular micronutrient intake. The authors integrate the most up-to-date understanding of human micronutrient requirements in this review.

Abstract

Many studies of micronutrient supplementation in developing countries have used single-nutrient supplements with either vitamins or minerals. However, people in these countries often suffer from multiple, rather than single, micronutrient deficiencies. The objective of this paper is to discuss the factors that go into determining the adequate dosing of vitamins and/or minerals for people of different ages. To elaborate on the adequacy of micronutrient doses in supplements, a model described by the US FNB was used, which calculates the difference between the mean observed intake for an individual and the estimated average requirement for a life stage and gender group. This model allows estimating the degree of confidence that a certain nutrient intake (from supplements and diet) is adequate. The US/Canadian DRI values have been used as the basis for these calculations, from which it can be concluded that a daily supplement of one RDA of each micronutrient is adequate to cover the personal requirements of all individuals in each respective age and gender group of the population, provided that 20 to 40% of an RDA is supplied by the diet—likely a realistic value for developing countries.

DRI values vary significantly between different age groups, reflecting changing needs over a life cycle. With the objective of a supplement to be adequate and safe, the design of a one-for-all supplement covering all age groups is not realistic. Such a supplement would either underscore or surpass the required intake of some of the age groups. Additionally the dosage of certain micronutrients might exceed the upper level of intake for lower age groups. Therefore, it is suggested that three different supplements following the one RDA concept for all micronutrients be developed for research use in developing countries for the following age groups: 1 to 3 years, 4 to 13 years, and females >14 years (excluding during pregnancy).

Key words: Deficiency, dosage, intervention, micronutrients, requirement, supplementation, vitamin/mineral

Introduction

Ideally, a sufficient and balanced diet should meet all of a person's micronutrient requirements. Unfortunately, large groups of people in deprived populations, such as in developing countries and in certain segments of industrialized countries, do not meet their requirements through diet. This may result in suboptimal intake of certain vitamins and minerals as well as severe clinical nutrient deficiencies [1]. Insufficient

Denise Bienz, Hector Cori, and Dietrich Hornig are affiliated with the Micronutrient Intervention Project, Roche Vitamins Ltd. in Basel, Switzerland. Address for correspondence: Denise Bienz, Roche Vitamins Ltd., CH-4070 Basel, Switzerland; phone: +41 64 688 5448; email: denise.bienz@roche.com.

food supply and/or food availability in many developing countries is strongly associated with micronutrient deficiencies. In addition, traditional and cultural variations as well as the wide variety of food patterns across countries and regions may be contributing factors.

Current research in industrialized countries is exploring the potential role of vitamins and minerals reducing risk for chronic, degenerative diseases such as cardiovascular disease, certain type of cancer, and eye diseases. These studies generally use single-entity vitamin supplements and study measurable endpoints, such as mortality or incidence of disease events. In developing countries, however, the main public health problem remains micronutrient undernutrition and deficiency. In these areas, the focus of research is to develop and implement strategies to provide adequate nutrition and micronutrients to the population. The observation that eliminating micronutrient deficiency will not only alleviate overt deficiency symptoms, but also will generally improve morbidity and reduce mortality of these populations was a major breakthrough. For example, correction of vitamin A deficiency in infants was demonstrated to not only prevent blindness but also to reduce significantly mortality in vitamin A–treated infants [2]. Similarly, elimination of iodine and iron deficiencies was shown to normalize overall development of infants and children [3, 4].

Many studies of micronutrient supplementation in developing countries have used single-nutrient supplements with either vitamins or minerals. But the people in these countries often suffer from multiple, rather than single, micronutrient deficiencies [5]. Additionally, it is well known that micronutrients act in concert and that many physiologic interactions exist between vitamins and minerals. To obtain maximum benefit, it is therefore necessary to supplement a balanced array of vitamins and minerals in an adequate combination. This makes multiple-micronutrient intervention the strategy of choice. A workshop convened by UNICEF/WHO/UNU has taken a similar approach previously and has made recommendations for the composition of a multi-micronutrient supplement to be used in pilot programs treating pregnant women in developing countries [6].

Various strategies have been developed and are currently in use to provide micronutrients to populations suffering from undernutrition. One strategy that has been shown to be successful in many instances is the fortification of staple foods, such as sugar, flour, or vegetable oil. This paper discusses another effective intervention strategy—supplementation with multivitamin/multimineral supplements. The objective of this paper is to discuss the factors that go into determining the adequate dosing of vitamins and/or minerals for people of different ages. The possibility of a "one-for-all" supplement, which includes multiple micronutrients, for use in research programs in developing countries will also be considered. Such a supplement would streamline operational strategies and distribution systems and perhaps lower costs, compared with programs using single-micronutrient supplements.

The most vulnerable groups within the life cycle are infants, small children (through adolescence), and women of childbearing age. Unfortunately, the scientific database particularly for the young age groups is insufficient and the knowledge of the daily requirements to prevent vitamin and mineral deficiencies is limited. Important factors to be considered in determining appropriate dosage levels are upper levels of intake and potential adverse effects related to supplementation in these age groups. In addition, the form of delivery (chewable tablet, tablet, capsule, syrup) and its impact on compliance and bioavailability must be considered.

Scientific basis for determination of dose

The US Food and Nutrition Board (FNB) of the Institute of Medicine, National Academy of Sciences, has recently developed a comprehensive set of reference values for dietary micronutrient intakes for all age and gender groups in a healthy population. All of the respective panel reports have been published or are available in pre-publication format [7–10]. Dietary reference intakes (DRI) are reference values that can be used for assessing and planning diets for healthy populations and for many other purposes. DRIs encompass the estimated average requirement (EAR), the recommended dietary allowances (RDA), the adequate intake (AI), and the tolerable upper level of intake (UL).

EAR is the nutrient intake that meets the requirement determined by a specified functional parameter in 50% of the individuals in a life stage and gender group, with the other 50% not meeting their micronutrient requirement. It is important to recognize that the EAR includes an adjustment for an assumed bioavailability of the respective nutrient.

The RDA is the average daily intake level that is sufficient to meet the nutrient requirement of 97% to 98% of individuals in a life stage and gender group and applies, therefore, to individuals. RDAs are calculated from the EAR using a coefficient of variation of mostly 10% (niacin 15%, vitamin A 20%), because data on variability in requirements are insufficient for most micronutrients.

The AI can be considered a surrogate for the RDA if insufficient scientific evidence is available to evaluate an EAR and to calculate a RDA. This is generally the case for infants up to one year of age and some children. AIs were also set for all age groups for several vitamins and minerals, including calcium, fluoride, vitamin D, vitamin K, pantothenic acid, and biotin. The AI is to

be used as a goal for the nutrient intake of individuals. Both the RDA and AI are micronutrient intake levels that should decrease the risk of developing a condition associated with a negative functional outcome, such as nutrient malnutrition or clinical nutrient deficiency state. However, intakes at the level of the RDA or AI replete undernourished individuals only over a longer period of time.

The UL is defined as the highest level of daily total chronic intake for a vitamin or mineral from food, fortified foods, and supplements that is likely to pose no risks of adverse health effects to almost all individuals in the general population. With high probability this intake level is biologically well tolerated and is therefore considered a safe intake. If adverse effects have been associated with intakes from fortified foods or supplements only, the UL is based on intake from those sources only. For some of the vitamins and minerals there are insufficient data available to set a UL, or no adverse effects have been described. In this case, no UL has been set. A UL was not determinable for infants up to 12 months of age due to lack of data on adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Also data to derive a UL for infants and adolescents were considered insufficient and in many cases a UL was extrapolated from those established for adults.

Recently, WHO has recognized that substantial segments of the population in developing countries are in a rapid transition toward considerable physical inactivity, overweight, and unbalanced nutrition contributing significantly to the current rise in chronic diseases. At the same time, control of undernutrition remains an unfinished work. Recognizing this development, the 53rd World Health Assembly (2000) adopted resolution WHA53.17 on the prevention and control of noncommunicable diseases, requesting WHO to continue to give this area high priority. WHO is taking steps to implement this global strategy.

Therefore, the US/Canadian DRI values have been used as the basis for this publication, because these values encompass the concept of micronutrient deficiency as well as risk reduction of chronic diseases by micronutrients.

Dosing of an appropriate supplement

Annex I gives an overview of the US/Canadian DRIs, subdivided by age groups and gender. The question arises if using one RDA for a daily multivitamin/multimineral supplement for populations in developing countries is the adequate dosing to meet the requirements of at least 97% of the population, or if an adjustment to a multiple or a fraction of the RDA would be more appropriate. This section elaborates on that question.

Considering that, even within a well-defined population, individuals vary greatly in their metabolism, activity level, and response to environmental exposures, it is obvious that their individual nutrient requirements may vary significantly. The fundamental question, therefore, is whether a person's diet is meeting his or her individual micronutrient requirements (defined as the lowest intake level to maintain a level of nutriture for a given criterion of nutritional adequacy). Figure 1 shows the assumed distribution of requirement and of intake of a particular micronutrient in a given population with the RDA covering the requirement of 97% to 98% of the individuals in that group. The more these two curves overlap, the higher the probability that an increasing number of individuals may no longer meet their personal requirements and that insufficient intakes cause micronutrient undernutrition or deficiency. Consequently, the objective of any micronutrient intervention strategy should be to shift the intake curve to sufficient high intakes, which also cover the variation of individual requirements. However, the requirement of an individual is mostly not known. Likewise, the individual's usual intake (average intake of a nutrient over a long period) is often not available or can only be determined by tedious procedures.

An approach that could be used to determine how large the difference (D) is between mean observed intake for an individual (y) and the requirement (EAR) for a life stage and gender group is described by the US FNB [11]. It gives the basis to conclude with a sufficient degree of confidence that the unobservable usual intake exceeds the unobservable actual requirement.

$$D = y - EAR$$

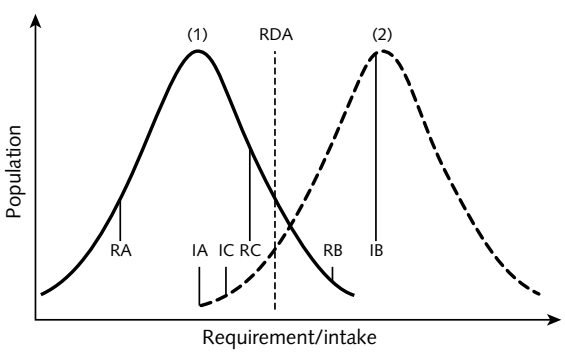


FIG. 1. Assumed (1) distribution of the requirement for a micronutrient in a population group and (2) distribution of intake for the same micronutrient in the same group. Requirement and intake of three hypothetical individuals are shown.
A: Intake is lower than the recommended intake (IA < RDA), but the requirement for this individual (RA) is covered.
B: Requirement is greater than the recommended intake (RB > RDA), but the intake is covered because IB > RB.
C: Requirement is below the recommended intake (RC < RDA), but because the intake is even lower than the requirement (IC < RC), this individual is at great risk for deficiency of this micronutrient.

To solve this question, one must know the following: (1) the variability of D (SD_D), (2) the standard deviation of the requirement (SD_{EAR}, assumed to be 10% for most nutrients), and (3) the within-person standard deviation (SD_{within}) of day-to-day intakes that can be estimated from large surveys of similar populations. The probability whether the intake is above (sufficient intake) or below (insufficient intake) the requirement can be determined by examining the ratio of $D:SD_D$.

To evaluate the adequate dosing for a supplement for malnourished populations, some assumptions are introduced. Because the population to be supplemented has a limited unknown micronutrient intake that will be mostly below or, at the most, close to the median requirement (EAR) as judged by the observed undernutrition, the dietary intake will not be taken into account. It will only be evaluated whether supplementation with, for example, one RDA (or AI) would be sufficient to cover the individual variation in requirement under consideration of the respective standard deviations. An example is given below for vitamin C:

Male adolescent, 13 years; duration of supplementation 180 days; EAR: 39 mg/day; SD_{EAR} = 3.9 mg/day; RDA: 45 mg/day; day-to-day variation in that age group (taken from Continuing Survey of Food Intakes by Individuals [CSFII]) : 81 mg/day.

By using the formula

$$SD_D = \sqrt{V_{EAR} + V_{within} / n}$$

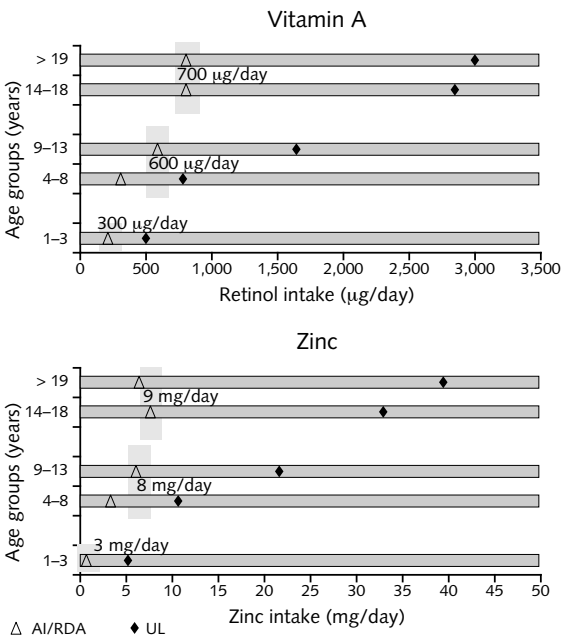
$$[V_{EAR} = (SD_{EAR})^2; V_{within} = (\text{within SD})^2; \\ n = \text{duration of supplementation}],$$

the SD_D yields 7.1 mg/day, and the ratio D: SD_D = (45 – 39)/7.1 = 0.45. That value implies a probability for a correct conclusion of 70% to 85% based on calculations by Snedecor and Cochran [12]. Thus, an intake of approximately 53 to 64 mg/day would be necessary to have confidence that intake is fully adequate. Because this model does not consider the ordinary dietary intake, one can assume that supplementation with one RDA is sufficient under this assumption, and that approximately 20% to 40% of the RDA (about 10 to 20 mg/day) is being consumed from the diet, in addition to the supplement. A similar calculation with 2 RDA will result in a D/SD_D of 7.1, implying 99% confidence that the chosen intake would be adequate. Adding only 50% of a RDA under the same assumptions will result in a D/SD_D of –2.3, implying that supplementation with only half the RDA is inadequate, and it would be uncertain whether the dietary intake could cover the difference.

This approach has several limitations. It does not take into account individual dietary intake, because it is unknown. The basis for the within-person standard deviation of intake is derived from the CSFII [12], which is conducted in the United States and may not be representative of individuals in micronutrient-deficient populations. In these groups, the within-subject variation might be much larger, leading to a lower D/SD_D ratio, indicating reduced confidence that the intake is adequate. Based on the above argumentation and calculations, it can be concluded that a supplement of one RDA of each micronutrient daily will mean that all individuals in each respective age group of the population will meet their personal requirements, if at least 20% to 40% of an RDA for the US/Canadian population is provided by dietary intake. This seems to be a realistic value for developing countries.

Feasibility of a "one-for-all" supplement

The availability of a one-for-all supplement in a life cycle group would provide significant logistic and programmatic advantages in research programs in developing countries. However, as demonstrated in Annex I, the recommended intake (RDA) and the upper level of intake (UL) vary substantially across different age groups. Figure 2 illustrates this for vitamin A and zinc, respectively. It also implies that a one-for-all supplement suitable for ages 1 to 13 years and >14 years (females, excluding pregnancy) either will



FIGS. 2a, 2b. RDA/AI (△) and UL (♦) values according to age groups for vitamin A and zinc, respectively [10]. The vertical axis represents age groups for females. Vertical bars indicate the suggested dosages for the life cycle–specific supplements for age groups 1 to 3 years (vitamin A 300 µg retinol/day ; zinc 3 mg/day), 4 to 13 years (vitamin A 600 µg retinol/day; zinc 8 mg/day), and >14 years (females, excluding pregnancy; vitamin A 700 µg retinol/day; zinc 9 mg/day).

underscore or surpass the required intake. Additionally, the dosage of certain micronutrients may exceed the upper level of intake (UL) for lower age groups where such an intake level has been defined. It is therefore suggested that three different supplements containing vitamins and minerals be developed for the life cycle groups 1 to 3 years, 4 to 13 years, and >14 years (females, excluding pregnancy). In order to assure the highest probability that the personal requirements of all individuals in a life cycle group are covered, the RDA of the age group with the highest requirement was selected. The composition of micronutrients in these supplements is based on the results of the UNICEF/WHO/UNU workshop [6] and a more recent workshop organized by the Ministry of Health, Brazil, and UNICEF in Rio de Janeiro [13]. In addition to these recommendations, it is suggested that vitamin K be included in such a supplement based on emerging results on the importance of this vitamin in bone health [14]. Table 1 summarizes the recommended dosage for these age-specific supplements suggested to be used in micronutrient research programs in developing countries.

Safety considerations

Supplementation with one RDA of micronutrients is not expected to create a nutrient imbalance. On the contrary, it is generally accepted that health protection could be achieved by establishing a better micronutrient status in a specific population. Several large intervention trials of micronutrient supplementation in the range of one RDA have demonstrated the overall safety of vitamins and minerals [15–17]. Nevertheless, safety considerations must be a specific component in each trial protocol and mechanisms must be in place to monitor any potential adverse effects during a trial. The US FNB has defined the UL as that daily chronic intake of a micronutrient that does not show any risk of adverse effect in the most sensitive part of a gender and age group. In fact, because the UL is derived in most cases from its NOAEL (no observed-adverse-effect-level) or for some micronutrients from its LOAEL (lowest-observed adverse-effect-level) it has already built in a margin of uncertainty regarding the strength of the overall data determining the NOAEL (or LOAEL). Defined as such, the UL is a safe intake. When compared with the RDA intake level, the UL is for most micronutrients a multiple of a RDA or AI (see Annex I). The FNB panels have used the National Health and Nutrition Examination Survey (NHANES) III data to elaborate on the likelihood of overconsumption due to supplementation of any content as available on the market in the United States and has recognized that no discernible portion of people consumed more than the UL. Therefore, in an undernourished population the risk for overconsumption of micronutrients is rather limited, even when supplemented with one RDA over longer periods of time. However, due to the often limited scientific data to derive the UL for several of the micronutrients for infants and children, these subjects should be closely monitored for any potential adverse effects during supplementation trials.

TABLE 1. Recommended dosages for 3 life-cycle specific supplements for age groups 1 to 3 years, 4 to 13 years, and > 14 years (females, excluding pregnancy) suggested to be used in micronutrient research programs in developing countries

Micronutrient	1 to 3 years	4 to 13 years	> 14 years
Vitamin A (μg)	300	600	700
Vitamin D (μg)	5	5	5
Vitamin E (mg)	6	11	15
Vitamin C (mg)	15	45	75
Vitamin K (μg)	30	60	90
Iron (mg)	7	10	18
Zinc (mg)	3	8	9
Copper (μg)	340	700	900
Iodine (μg)	90	120	150
Thiamine (mg)	0.5	0.9	1.1
Riboflavin (mg)	0.5	0.9	1.1
Vitamin B_6 (mg)	0.5	1.0	1.3
Niacin (mg)	6	12	14
Folate (μg DFE)	150	300	400
Vitamin B_{12} (μg)	0.9	1.8	2.4

Conclusion

Interventions of multiple-micronutrient supplements, rather than single-nutrient supplements, may be the strategy of choice to be pursued in selected age and gender groups, such as young children and adolescents, to combat micronutrient undernutrition or deficiency states in developing countries. In this context, the question of composition and adequate dosing of vitamins and/or minerals for different age groups in the life cycle arises. Optimally, a "one-for-all" supplement preparation should be designed for general use in research programs in developing countries. It should include the following nutrients: vitamins A, D, E, B_1, B_2, B_6, B_{12}, C, folic acid, and niacin; and minerals iron, zinc, copper, and iodine. More recent research has indicated that vitamin K should also be included.

For the determination of adequate dosing, two main approaches were used: (1) The US FNB's new DRIs were an excellent and most recent scientific compilation for intake recommendations (RDA/AI) and for upper levels of intake (UL), and (2) The personal requirements and dietary intakes of individuals

within a specific population were considered when these reference values were applied in the design of an adequate supplement. Unfortunately, in most cases, neither the personal requirement of an individual for a micronutrient nor his or her usual intake was known. By using a model recently described by the US FNB and by employing standard deviations of requirement and within-person standard deviations, one can determine with a high degree of confidence whether supplementation with one RDA is sufficient to secure that all individuals in these populations will meet their personal requirements. Based on these calculations, it can be concluded that a multivitamin/multimineral supplement containing one RDA of each micronutrient is adequate to cover the individual requirements of a population, provided that 20% to 40% of the RDA is supplied by the diet—likely a realistic value for developing countries.

DRI values vary significantly between different age groups, reflecting the changing needs over a life cycle. The overall objective of a supplement is to be adequate and safe. Consequently, the design of a one-for-all supplement for covering all age groups is not realistic and would either underscore or surpass the required intake. Therefore, it is suggested that three different supplements following the one-RDA concept for all micronutrients be developed for use in research in developing countries for the following age groups: 1 to 3 years, 4 to 13 years, and females >14 years (excluding pregnancy). The UL can be used to estimate the likelihood of potential adverse effects of micronutrients. Because the UL is a multiple of the RDA or AI for most micronutrients, the risk for overconsumption is rather limited in an undernourished population, even when supplementation with one RDA over longer periods of time occurs.

References

1. Stephenson LS, Latham MC, Ottesen EA. Global malnutrition. Parasitology 2000;121:S5–22.
2. Sommer A, West KP Jr. Vitamin A deficiency: Health, survival, and vision. New York: Oxford University Press, 1996.
3. WHO/UNICEF, International Council for Control of Iodine Deficiency Disorders (ICCIDD). Indicators for assessing iodine deficiency disorders and their control through salt iodization. Geneva: World Health Organization, 1994.
4. WHO/UNICEF/UNU. IDA: Prevention, assessment, and control: report of a joint WHO/UNICEF/UNU consultation. Geneva: World Health Organization, 1998.
5. WHO. The world health report: report of the Director-General. Geneva: World Health Organization, 1998.
6. UNICEF. Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries: proceedings of a joint UNICEF/UNU/WHO workshop, July 1999. New York: UNICEF, 2000.
7. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington DC: National Academy Press, 1997.
8. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington DC: National Academy Press, 1998.
9. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington DC: National Academy Press, 2000.
10. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington DC: National Academy Press, 2001 (as pre-publication).
11. Subcommittee on Interpretation and Use of Dietary Reference Intakes and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Application in dietary assessment. Washington DC: National Academy Press, 2001; pp 45–69.
12. Subcommittee on Interpretation and Use of Dietary Reference Intakes and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Application in dietary assessment. Washington DC: National Academy Press, 2001; pp 185–202.
13. Gross R, ed. Micronutrient supplementation throughout the life cycle: report of a workshop held by the Ministry of Health, Brazil, and UNICEF. New York: UNICEF, 2001.
14. Weber P. Vitamin K and bone health. Nutrition 2001;17: 880–7.
15. Li JY, Taylor R, Li B, Dawsey S, Wang GQ, Ershow AG, Guo W, Liu SF, Yang CS, Shen Q. Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. J Natl Cancer Inst 1993;85:1492–8.
16. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II: randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. Ann Epidemiol 2000;10:125–34.
17. Hercberg S, Preziosi P, Briançon S, et al. A primary prevention trial using nutritional doses of antioxidant vitamins and minerals in cardiovascular diseases and cancers in general population: the SU.VI.MAX study—design, methods and participant characteristics. Control Clin Trials 1998;19:336–51.

ANNEX I: DRI values (Calcium Panel Report 1997; B-Vitamins and Choline Panel Report 1998; Dietary Antioxidant Panel Report 2000; Vitamin A, Vitamin K, Trace Elements Panel Report 2001). Indicated are ranges depending on gender and age.

Nutrient	RDA	AI	UL
Children (1–3 years)			
Vitamin B_1	0.5 mg	—	None
Vitamin B_2	0.5 mg	—	None
Niacin	6 mg NE	—	10 mg NE
Vitamin B_6	0.5 mg	—	30 mg
Folate	150 µg DFE*	—	300 µg folic acid, none for folate from food
Vitamin B_{12}	0.9 µg	—	None
Vitamin C	15 mg	—	400 mg
Pantothenic Acid	None	2 mg	None
Biotin	None	8 µg	None
Vitamin A	300 µg	—	600 µg
Vitamin D	None	5 µg (200 IU)	50 µg (2000 IU)
Vitamin E	6 mg**	—	200 mg***
Vitamin K	—	30 µg	None
Calcium	None	500 mg	2500 mg
Phosphorus	460 mg	—	3.0 g
Magnesium	80 mg	—	65 mg****
Fluoride	None	0.7 mg	1.3 mg
Copper	340 µg	—	1000 µg
Iodine	90 µg	—	200 µg
Iron	7 mg	—	40 mg
Zinc	3 mg		7 mg
Selenium	20 µg	—	90 µg
Children (4–8 years)			
Vitamin B_1	0.6 mg	—	None
Vitamin B_2	0.6 mg	—	None
Niacin	8 mg NE	—	15 mg NE
Vitamin B_6	0.6 mg	—	40 mg
Folate	200 µg DFE*	—	400 µg folic acid, none for folate from food
Vitamin B_{12}	1.2 µg	—	None
Vitamin C	25 mg	—	650 mg
Pantothenic Acid	None	3 mg	None
Biotin	None	12 µg	None
Vitamin A	400 µg	—	900 µg
Vitamin D	None	5 µg (200 IU)	50 µg (2000 IU)
Vitamin E	7 mg **	—	300 mg***
Vitamin K	—	55 µg	None
Calcium	None	800 mg	2500 mg
Phosphorus	500 mg	—	3.0 g
Magnesium	130 mg	—	110 mg****
Fluoride	None	1.0 mg	2.2 mg
Copper	440 µg	—	3000 µg
Iodine	90 µg	—	300 µg
Iron	10 mg	—	40 mg
Zinc	5 mg	—	12 mg
Selenium	30 µg	—	150 µg

continued

ANNEX I: DRI values (Calcium Panel Report 1997; B-Vitamins and Choline Panel Report 1998; Dietary Antioxidant Panel Report 2000; Vitamin A, Vitamin K, Trace Elements Panel Report 2001). Indicated are ranges depending on gender and age. *(continued)*

Nutrient	RDA	AI	UL
Children (9–13 years)			
Vitamin B_1	0.9 mg	—	None
Vitamin B_2	0.9 mg	—	None
Niacin	12 mg NE	—	20 mg NE
Vitamin B_6	1.0 mg	—	60 mg
Folate	300 µg DFE*	—	600 µg folic acid, none for folate from food
Vitamin B_{12}	1.8 µg	—	None
Vitamin C	45 mg	—	1200 mg
Pantothenic Acid	None	4 mg	None
Biotin	None	20 µg	None
Vitamin A	600 µg	—	1700 µg
Vitamin D	None	5 µg (200 IU)	50 µg (2000 IU)
Vitamin E	11 mg**	—	600 mg***
Vitamin K	-	60 µg	None
Calcium	None	1300 mg	2500 mg
Phosphorus	1250 mg	—	4.0 g
Magnesium	240 mg	—	110 mg****
Fluoride	None	2.0 mg	10 mg
Copper	700 µg	—	5000 µg
Iodine	120 µg	—	600 µg
Iron	8 mg	—	40 mg
Zinc	8 mg	—	23 mg
Selenium	40 µg	—	280 µg
Adolescents (14–18 years)			
Vitamin B_1	1.2 / 1.0 mg°	—	None
Vitamin B_2	1.3 / 1.0 mg°	—	None
Niacin	16 / 14 mg NE°	—	30 mg NE
Vitamin B_6	1.3 / 1.2 mg°	—	80 mg
Folate	400 µg DFE*	—	800 µg folic acid, none for folate from food
Vitamin B_{12}	2.4 µg	—	None
Vitamin C	75 mg / 65 mg	—	1800 mg
Pantothenic Acid	None	5 mg	None
Biotin	None	25 µg	None
Vitamin A	900 / 700 µg°	—	2800 µg
Vitamin D	None	5 µg (200 IU)	50 µg (2000 IU)
Vitamin E	15 mg **	—	800 mg***
Vitamin K	—	75 µg	None
Calcium	None	1300 mg	2500 mg
Phosphorus	1250 mg	—	4.0 g
Magnesium	410 / 360 mg°	—	350 mg****
Fluoride	None	3.0 mg	10 mg
Copper	890 µg	—	8000 µg
Iodine	150 µg	—	900 µg
Iron	11 / 15 mg°	—	45 mg
Zinc	11 / 9 mg°	—	34 mg
Selenium	55 µg	—	400 µg

continued

ANNEX I: DRI values (Calcium Panel Report 1997; B-Vitamins and Choline Panel Report 1998; Dietary Antioxidant Panel Report 2000; Vitamin A, Vitamin K, Trace Elements Panel Report 2001). Indicated are ranges depending on gender and age. *(continued)*

Nutrient	RDA	AI	UL
Adults (19–50 years)			
Vitamin B_1	1.2 / 1.1 mg°	—	None
Vitamin B_2	1.3 / 1.1 mg°	—	None
Niacin	16 / 14 mg NE°	—	35 mg NE
Vitamin B_6	1.3 / 1.3 mg°	—	100 mg
Folate	400 µg DFE*; 600 µg DFE* (pregnancy)+	—	1,000 µg (synth.), none for folate from food
Vitamin B_{12}	2.4 µg++	—	None
Vitamin C	90 mg / 75 mg	—	2000 mg
Pantothenic Acid	None	5 mg	None
Biotin	None	30 µg	None
Vitamin A	900 / 700 µg°	—	3000 µg
Vitamin D (19–50 y)	None	5 µg (200 IU)	50 µg (2,000 IU)
Vitamin E	15 mg **	—	1,000 mg***
Vitamin K	—	120 / 90 µg°	None
Calcium	None	1000 mg	2,500 mg
Phosphorus	700 mg	—	4.0 g
Magnesium (19–30 y; >31 y)	400 / 310 mg°; 420 / 320 mg°	—	350 mg (non-food only)
Fluoride	None	4 / 3 mg°	10 mg
Copper	900 µg	—	10,000 µg
Iodine	150 µg	—	1100 µg
Iron	8 / 18 mg°	—	45 mg
Zinc	11 / 8 mg°	—	40 mg
Selenium	55 µg	—	400 µg

* DFE = dietary folate equivalents = 1 µg food folate = 0.5 µg synthetic folic acid on empty stomach = 0.6 µ synthetic folic acid with meals

** vitamin E activity of α-tocopherol is defined to be limited to the naturally occurring form RRR- and the other 3 synthetic 2R-stereoisomer forms RSR-, RRS-, and RSS- of α-tocopherol

*** of any form of supplementary α-tocopherol

**** supplementary magnesium

\+ in addition to dietary folate 400 µg of folic acid as supplement is recommended for women capable of becoming pregnant to reduce the risk of neural tube defects

++ adults > 51 years are advised to obtain most of this amount by taking foods fortified with vitamin B_{12} or vitamin B_{12} – containing supplements

° males / females

The foodLET vehicle designed for and used in the IRIS I intervention

Gabriela Lock

Editors' Note

The format for delivering infant supplementation recommended at the 1999 Rio de Janeiro workshop was a food-like vehicle that would be a hybrid of a cookie and a tablet. Such a foodlet had never been engineered or manufactured up to that point. An experienced international vitamin supplier (Roche) and a local pharmaceutical company in Lima (Hersil, S.A.) collaborated in the manufacturing and production of this foodlet. They produced the prototype and then went on to produce coded, masked supplies to provide almost 1000 infants in four developing countries with 180 days' worth of foodlets. This paper documents the process.

Abstract

At the behest of UNICEF, conceptual specifications from the International Workshop on Micronutrient Supplementation throughout the Life Cycle (held in Rio de Janeiro, Brazil, in November 1999) were developed for a chewable, flavored multiple-micronutrient vehicle that was a hybrid of a food and a tablet (i.e., "foodLET"). Two varieties of foodLET were created: one with a single infant–toddler RDA for selected micronutrients, and the other with two RDAs for the same vitamins and minerals. They were shipped and stored in special, hermetic blister packs to protect the physical form from crumbling and to protect the vitamins from oxidative damage. In the actual experience of delivering more than 40,000 foodLETs in four sites in diverse settings, the ability of the product to live up to the ideal characteristics can be assessed.

Key words: blister pack, foodlet, infant nutrient requirements, micronutrients

Gabriela Lock is Human Nutrition & Health Manager and Director at Roche Vitamins Peru S.A. Address for correspondence: Roche Vitaminas Peru S.A., Av. Javier Prado Este, 1921, San Borja / Lima, Casilla de Correo 41-018, Lima, Peru; email: gabriela.lock@roche.com.

Introduction

Micronutrient deficiencies are a worldwide problem [1]. Certain population groups are more vulnerable than others, and infants and toddlers are among the most susceptible because of their rapid rates of growth as well as their low-nutrient-density diets and the often poor bioavailability of micronutrients in traditional complementary (weaning) foods [2, 3]. The growth retardation observed in early life in low-income societies may be due to deficiency of one or more essential vitamins or minerals [4].

The International Workshop on Micronutrient Supplementation throughout the Life Cycle, convened in November 1999 in Rio de Janeiro, Brazil, responded to this problem. The ideas generated at this meeting centered on the dosing of supplemental micronutrients, both in the dosages of nutrients and the delivery vehicles [5]. The meeting participants reached a consensus as to the ideal characteristics for a supplementation vehicle to administer to infants just completing exclusive breast-feeding at 6 months of age and entering the period of complementary feeding. These characteristics are listed in table 1.

The vehicle chosen for the International Research on Infant Supplementation (IRIS I) multicenter intervention was to be a food-like tablet, or "foodLET." All of the foodLETs used in each of the four sites (Peru,

TABLE 1. Characteristics of the vehicle required for IRIS I

- » Chewable by children, with an acceptable flavor
- » Soft enough to be crumbled and combined with meals, such as being mixed with whatever an infant or child is eating
- » Modest-to-high solubility
- » Water dispersible, so that it can be given in any liquid the infant or child is drinking
- » Easy to dose
- » Stable
- » Good physical resistance
- » Acceptable shelf life
- » Affordable cost

South Africa, Indonesia, and Vietnam) were produced in Lima, Peru, through a collaboration between Roche and Hersil, SA in that location.

Nutrient levels

The foodLET provided 100% of the daily requirements (1 RDA) for infants and small children of the following nutrients: vitamins A, D, E, C, B_1, B_2, B_6, B_{12}, niacin, folic acid, iron, zinc, copper, and iodine. A thorough rationale for this formulation strategy was discussed at the Lima meeting, May 30–June 1, 2001, and is presented elsewhere in these proceedings by Bienz et al. [6]. We formulated the foodLET with suitable overages to compensate for storage loss through the expected shelf life of the product and its use in the tropical environments of Vietnam and Indonesia. Excipients were added to produce the suitable texture and flavor as well as for technical purposes. The formulation of the foodLET for the single RDA, six-days-per-week arm of the IRIS I intervention is shown in table 2.

The IRIS I protocol encompassed four treatment groups. In one of the groups, micronutrients were to be provided once per week in a dose of 2 RDAs. This required the development of an alternate formulation. However, because this was a randomized and double-blind field trial, the nutrients had to be compacted into a foodLET that was of the same size and weight as the 1-RDA foodLET. Table 3 provides the details on this formulation. All of the B-complex vitamins in these formulations were commercial forms of high solubility. The fat-soluble vitamins were highly water-dispersible forms. The source of minerals was chosen considering organoleptic and bioavailability issues. The total weight for both the 1- and 2-RDA foodLETs was 2,800 mg with a diameter of 20 mm.

Storage and packing

Packing requirements were rigorous. Because of the relatively soft nature of the foodLET, we chose blister packs as the most suitable method of packaging. This keeps oxygen out of the product and provides adequate physical protection. Figure 1 shows the blister pack used in the IRIS I study, with seven units, one at the point and to be taken first, which was either the 2-RDA dose or its placebo, and the remaining six, which were daily doses of either nutrients or placebos.

TABLE 2. FoodLET formulation containing one RDA

Ingredient	Amount
Vitamins	
Vitamin A	375 μg retinol equivalents (1250 IU)
Vitamin D	5 μg
Vitamin E	6 mg α-tocopherol
Vitamin C	35 mg
Vitamin B_1	0.5 mg
Vitamin B_2	0.5 mg
Vitamin B_6	0.5 mg
Vitamin B_{12}	0.9 μg
Niacin	6 mg
Folate	150 μg
Minerals	
Iron	10 mg
Zinc	10 mg
Copper	0.6 mg
Iodine	59 μg
Inactive ingredients	
Milk solids	
DiPac sugar	
Confectionery sugar	
Fructose	
Flavor	
Citric acid	
Calcium carbonate	
Magnesium stearate	
Total tablet weight: 2800 mg	

TABLE 3. FoodLET formulation containing two RDAs

Ingredient	Amount
Vitamins	
Vitamin A	750 μg retinol equivalents (2500 IU)
Vitamin D	10 μg
Vitamin E	12 mg α-tocopherol
Vitamin C	70 mg
Vitamin B_1	1.0 mg
Vitamin B_2	1.0 mg
Vitamin B_6	1.0 mg
Vitamin B_{12}	1.8 μg
Niacin	12 mg
Folate	300 μg
Minerals	
Iron	20 mg
Zinc	20 mg
Copper	1.2 mg
Iodine	118 μg
Inactive ingredients	
Milk solids	
DiPac sugar	
Confectionery sugar	
Fructose	
Flavor	
Citric acid	
Calcium carbonate	
Magnesium stearate	
Total tablet weight: 2800 mg	

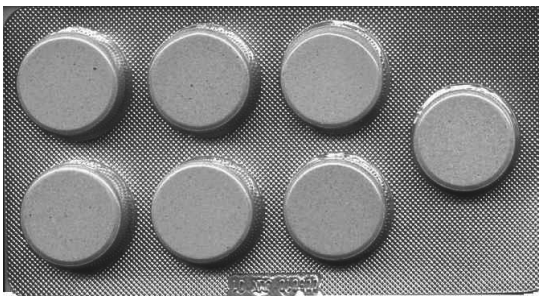


FIG 1. A blister pack containing seven of the 2800 mg, 20 mm diameter foodLETs

Fulfilling the foodLET promise

The supplementation aspect of the 1999 workshop in Rio de Janeiro addressed the difficulties in delivering micronutrients to infants and young children due to their difficulty in swallowing tablets or capsules and the instability of liquid syrups. Something closer to the chemical and cultural nature of food was deemed necessary, and the foodLET was the resulting product.

By the time workshop participants met again in Lima in 2001, the IRIS field studies in all four sites had been concluded, including more than 1,500 subject-months of delivery of foodLET. Through the design emerging from the Rio meeting, two years earlier, we had created a big tablet that was less "hard" than usual, enabling children as young as 6 months old to suck or chew the tablet. In fact, according to the investigators, the foodLET was harder than would have been ideal. At the South African site, the foodLET was actually disintegrated and mixed into porridge [7].

The nutrients in the foodLET were soluble and water dispersible. Bioavailability studies performed in Rio de Janeiro research laboratories [8] confirmed adequate bioavailability of selected nutrients within the foodLET formulation.

The combination of an acceptable flavor and citric acid reduced the off flavor that minerals sometimes produce. In practice, the foodLET was easy to dose and proved to be stable. The blister pack generally preserved the integrity of the product. Some blister packs contained crushed tablets upon delivery at some sites, but this did not influence the execution of the intervention.

With respect to cost and affordability, one can never really extrapolate from the situation of an intensive and controlled experimental field study what a product would cost and sell for in the real world of public health programs. The seven-unit blister pack in figure 1 is not the one used in the IRIS I trial, but a simpler one modeled for commercial sales. Indeed, protecting a product that is meant to crumble on—but not before—use requires investment in special packaging. And, as stated, the minerals used were from compounds of higher solubility and better organoleptic properties, which are more expensive than more common soluble salts. However, if the promise of efficacy of a weekly delivery of a 2-RDA variety is demonstrated, overall program costs will be competitive compared with daily administration of a less well-crafted product.

Conclusion

The foodLET is a flexible product, created in response to an innovative approach to public health nutrition for young children, which grew out of a workshop held in 1999 in Rio de Janeiro [5]. Less than 2 years later, we were able to examine the experience in a follow-up workshop held in Lima, Peru. The first production for the field trial met most of the parameters required by the workshop participants. We know that the composition of a foodLET can be modified according to the proportion of the RDA that is required to be delivered, the required micronutrient composition, and the intake reference to be used. The foodLET has been met with great enthusiasm as a potential format for infant supplementation. At the same time, we continue to refine the ideal dosage and dosing schedule that will be most safe, effective, and cost-efficient for the prevention of multiple-micronutrient malnutrition in young children in poor societies.

Acknowledgements

Thanks to Guillermo Silva for his contributions to food technology work on the foodLETs and in the preparation of the presentation at the Lima workshop. Thanks to Hersil, SA, the pharmaceutical house in Lima that produced the foodLETs for IRIS I distribution, and to Dr. Noel Solomons for his contributions to this manuscript.

References

1. Trowbridge FL, Harris SS, Cook J, Dunn JT, Florentino RF, Kodyat BA, Mannar MG, Reddy V, Tontistrin K, Underwood BA, Yip R. Coordinated strategies for controlling micronutrient malnutrition: A technical workshop. J Nutr 1993;123:775–87.
2. Brown KH, Dewey KG, Allen LH. Complementary feeding of young children in developing countries. New York: UNICEF, 1998.
3. Brown KH, Dewey KG. Update on technical issues concerning complementary feeding of young children in

developing countries and implications for intervention programs. Food Nutr Bull 2003;24:5–28.
4. Allen LH. Nutritional influences on linear growth. Eur J Clin Nutr 1994;48(Suppl 1):S75–89.
5. Gross R. Micronutrient supplementation throughout the life cycle. New York: UNICEF, 2001.
6. Bienz D, Cori H, Hornig D. Adequate dosing of micronutrients for different age groups in the life cycle. Food Nutr Bull 2003;24:S7–S15.
7. Smuts CM, Benadé AJS, Berger J, Hop LT, López de Romaña G, Untoro J, Karyadi E, Erhardt J, Gross R. IRIS I: A foodlet-based multiple-micronutrient intervention in 6- to 12-month-old infants at high risk of micronutrient malnutrition in four contrasting populations: Description of a multicenter trial. Food Nutr Bull 2003;24:S27–S33.
8. Kamp F, Jandel D, Hoenicke I, Pietrzk K, Gross R, Trugo NMF, Donangelo CM. Bioavailability of iron, zinc, folate, and vitamin C in the IRIS multi-micronutrient supplement: Effect of combination with a milk-based cornstarch porridge. Food Nutr Bull 2003;24:S20–S26.

Bioavailability of iron, zinc, folate, and vitamin C in the IRIS multi-micronutrient supplement: Effect of combination with a milk-based cornstarch porridge

Fernanda Kamp, Doris Jandel, Imke Hoenicke, Klaus Pietrzk, Rainer Gross, Nadia M.F. Trugo, and Carmen M. Donangelo

Editors' Note

This paper provides data from controlled metabolic studies to examine the biological availability of indicator micronutrients within the multinutrient mixture incorporated into the novel foodlet. One limitation of this research is that the subjects were healthy urban adults and the intended subjects of the IRIS research were infants and toddlers from 6 to 18 months old. Ethical and time constraints prevented examination of bioavailability of the component micronutrients of the IRIS foodlet in young children. Because unforeseen circumstances would make it necessary in the African site for the foodlet to be crushed into porridge rather than taken on an empty stomach, it was fortunate to have already demonstrated that the matrix of the food-like tablet could easily release the nutrients from the adult human intestine into the circulation. The IRIS teams used these findings to assure themselves that they had a product with the likely ability to deliver its nutrients to young children before the field research began around the world.

Abstract

The effect of combining a multi-micronutrient supplement with a milk-based cornstarch porridge on the bioavailability of iron, zinc, folate, and vitamin C was evaluated using the plasma curve response over time (8 hours) in healthy women. Three tests were carried out in a crossover design: S (multi-micronutrient supplement), MS (multi-micronutrient supplement plus test meal), and M (test meal). Relative bioavailability was determined as the percent ratio of the area under the curve (AUC) in MS corrected by M, and AUC in S. Compared to S, AUC in MS was smaller for iron ($p < .05$), for zinc ($p < .01$), and for folate ($p < .05$), but not different for vitamin C. Relative bioavailability was lower ($p < .05$) than 100% for iron (80%), zinc (70%), and folate (85%). The decrease in bioavailability of these nutrients when the multi-micronutrient supplement is combined with a milk-based cornstarch porridge is small. Therefore, the tested meal is a suitable vehicle for the multi-micronutrient supplement.

Key words: bioavailability, folate, iron, multi-micronutrient supplement, porridge, vitamin C, zinc

Introduction

Iron-deficiency anemia is a major problem in developing countries, especially in infants, preschool children, and women of childbearing age [1]. Other micronutrient deficiencies usually coexist with iron deficiency because of poor dietary quality, reduced nutrient bioavailability, and high incidence of infection. The coexistence of several micronutrient deficiencies may increase the risk of anemia and limit the hematologic response to iron supplementation [2], and may result in other health problems with adverse consequences, particularly in infants and young children.

Zinc deficiency in infants and young children causes growth retardation, abnormal immune function, and impairment of cognitive function [3]. Folate is essential for nucleic acid synthesis and amino acid metabolism [4]; deficiency of folate affects cellular division and may have serious consequences on growth and development in infants. Vitamin C deficiency in infants (an often neglected problem) may result in impaired bone growth and hemorrhagic anemia [5]. Because vitamin C is a strong enhancer of nonheme-iron absorption, vitamin C deficiency may also decrease the bioavail-

Fernanda Kamp, Nadia M.F. Trugo, and Carmen M. Donangelo are affiliated with the Laboratório de Bioquímica Nutricional e de Alimentos, Instituto de Química, Universidade Federal in Rio de Janeiro, Brazil; Doris Jandel, Imke Hoenicke, and Klaus Pietrzk are affiliated with the Universität Bonn in Germany; Rainer Gross is affiliated with UNICEF in New York City, USA. Address for correspondence: Carmen M. Donangelo, Instituto de Química, UFRJ, CT, Bloco A, Cidade Universitária, 21949-900 Rio de Janeiro, Brazil; email: donangel@iq.ufrj.br.

ability of dietary nonheme iron [5].

Because multiple micronutrient deficiencies often coexist, the benefit of multiple-micronutrient supplementation is becoming increasingly apparent. Recent international workshops have yielded a recommendation for using multi-micronutrient supplements to treat and prevent multiple micronutrient deficiencies in high-risk groups in developing countries, including women of childbearing age [6] and infants and young children [7]. During the workshop on "Micronutrient supplementation throughout the life cycle" held in Brazil in November, 1999 [7], a multi-micronutrient supplement was proposed for use in infants 6 to 24 months of age (preferably administered with an appropriate infant food to ensure acceptability and complete intake). To evaluate the efficiency of this multi-micronutrient supplement, a multicenter study (International Research on Infant Supplementation or IRIS) was carried out in four different developing countries.

Micronutrient interactions (synergistic or antagonistic) can occur with the use of multi-micronutrient supplements, depending on the specific combination of nutrients, their chemical forms, and relative doses [8]. These interactions may influence the bioavailability of each micronutrient, which may be further affected by the simultaneous ingestion of food [8]. Therefore, if a multisupplement is to be combined with food, the effect of the selected food on micronutrient bioavailability must be tested.

The present study evaluated how combining the IRIS multi-micronutrient supplement with a milk-based cornstarch porridge affected the bioavailability of iron, zinc, folate, and vitamin C. The study was conducted in healthy women and used the plasma curve response over time. Healthy women were chosen as the study population because it would have been unethical to use infants and young children. Porridge was selected as a food vehicle because it is commonly used as a complementary food during weaning in many countries.

TABLE 1. Composition of the IRIS multi-micronutrient supplement

Ingredients	Dose per tablet
Vitamin A	375 μg RE (as retinyl acetate)
Vitamin D	5 μg
Vitamin E	6 mg (as α-tocopherol)
Vitamin K	10 μg
Vitamin C	35 mg
Vitamin B_1	0.5 mg
Vitamin B_2	0.5 mg
Vitamin B_6	0.5 mg
Vitamin B_{12}	0.9 μg
Niacinamide	6 mg
Folic acid	150 μg
Iron	10 mg (as ferrous fumarate)
Zinc	10 mg (as zinc citrate)
Copper	0.6 mg (as cupric oxide)
Iodine	59 μg (as potassium iodide)

Subjects and methods

Subjects

Bioavailability tests were conducted in 10 healthy female volunteers recruited among students and faculty at Universidade Federal do Rio de Janeiro in Brazil. Subjects were between the ages of 23 and 50, without a recent history of supplement or medication use. Subjects filled out questionnaires with information on body weight, height, and medical history. Habitual dietary intakes were assessed from 3-day dietary records, and nutrient intakes were determined using *The Food Processor* (ESHA Research, OR, USA). The women maintained their normal dietary habits during the study. All subjects gave written informed consent.

Study design

A randomized crossover design was used. Each volunteer was submitted to three tests: (1) IRIS multi-micronutrient supplement (S), (2) IRIS multi-micronutrient supplement with test meal (MS), and (3) test meal (M). The dose of the multi-micronutrient supplement was five tablets per volunteer. The composition per tablet is described in table 1. The test meal consisted of one serving of cornstarch porridge. The ingredients and nutrient composition of the test meal are shown in table 2. One serving of this meal is a poor source of zinc, iron, and folate, and it contains no vitamin C.

TABLE 2. Composition of the test meal

	Amount per serving (300 ml)
Ingredients	
Whole milk, dry powdered	32 g
Sugar	30 g
Cornstarch (Maizena®)	30 g
Cinnamon	0.7 g
Nutrient composition	
Energy	397 kcal
Protein	8.6 g
Fat	8.5 g
Carbohydrate	71 g
Dietary fiber	0.6 g
Calcium	329 mg
Zinc	1.1 mg
Iron	0.6 mg
Folate	11 μg

The tests were carried out after overnight fast on three different days with a washout period of one week between the test days. On the morning of the test day, an intravenous catheter was inserted into the antecubital vein and a baseline blood sample was obtained (10 ml). Each of the tests—S, MS, or M—was ingested with 200 ml of water, and sequential blood draws (10 ml) were done at 1, 2, 3, 4, 6, and 8 hours after ingestion. At 2 to 3 hours and 6 to 7 hours, subjects each received an identical snack of white bread, butter, and fruit jam.

Laboratory analysis

Hemoglobin concentration and hematocrit were measured in whole blood by the cyanmethemoglobin method using a commercial kit (Bioclin) and by capillary centrifugation, respectively. An aliquot of whole blood (100 µl) was diluted 20-fold in 2% ascorbic acid for determination of erythrocyte folate. Plasma was separated by centrifugation. Aliquots of diluted blood and plasma samples were stored at –70º C until analysis. Plasma iron and plasma zinc were measured by inductively coupled plasma atomic emission spectrometry (ICP-AES, Perkin Elmer Plasma 1000). Plasma and erythrocyte folate were determined by radioisotope dilution assay using a commercial kit (Diagnostic Products Corporation, EUA). Plasma vitamin C was measured by a colorimetric assay using dinitrophenylhydrazine [9].

Calculation of relative bioavailability

The increment in plasma micronutrient concentration at each time point was calculated by the difference between plasma concentration at the corresponding time point and baseline plasma concentration. The increments in plasma concentrations were plotted versus time. The area under the curve (AUC) during 8 hours was calculated according to the trapezoidal method [10], using the following formula: $AUC = \frac{1}{2}\Sigma (\Delta C_{i-1} + \Delta C_i) \times (t_i - t_{i-1})$, where ΔC_i and ΔC_{i-1} are the increment plasma micronutrient concentrations at time points t_i and t_{i-1}. The AUC would become negative if the plasma nutrient concentration fell below the baseline level. The relative bioavailability of each micronutrient was determined from the ratio between AUC of MS corrected by M and the AUC of S, expressed as a percentage.

Statistical analysis

For each micronutrient, within-subject differences between S and MS for AUC, maximum increment in plasma concentration (ΔC_{max}), and time to reach maximum increment were tested by paired-t test. One-sided t-test was used to compare relative bioavailability with 100%. Results were considered significant when $p < 0.05$.

Results

Subjects' characteristics, including biochemical indices and habitual dietary intake of the micronutrients studied, are summarized in table 3. Although mean intakes of iron, zinc, and folate were 62%, 81%, and 54% of recommended values, respectively, [11], the corresponding biochemical indices of status were, on average, adequate [12]. Vitamin C intake and status were adequate in all subjects.

Figure 1 shows the mean increments in plasma concentrations at each time point after ingestion of S, MS, and M for iron, zinc, folate, and vitamin C. The magnitude of responses in plasma increments after intake of S, calculated from the ratio between the mean ΔC_{max} and the mean baseline plasma concentration for each micronutrient, was 4.9 for folate, 0.9 for iron and for zinc, and 0.4 for vitamin C. A considerable negative AUC for zinc was observed in M. The effect of food intake on plasma zinc concentrations is well documented and can be explained by zinc uptake by the liver after a meal [13, 14].

Table 4 shows the means of the individual values of AUC, maximum increments in plasma concentrations (ΔC_{max}), and time to reach this maximum for the micronutrients studied in each test. Compared to the multi-micronutrient supplement alone (S), AUC and ΔC_{max} in the test with the multi-micronutrient supplement combined with the test meal (MS) were significantly lower for iron, zinc, and folate. However, for vitamin C there were no differences between MS and S. The period of time to reach maximum increment in

TABLE 3. Characteristics of subjects ($n = 10$)

Characteristic	Mean ± SD
Age (years)	28 ± 8
BMI (kg/m^2)	21.2 ± 2
Habitual Dietary Intake	
Iron (mg/day)	11.1 ± 3.5
Zinc (mg/day)	6.5 ± 2.1
Folate (µg/day)	216 ± 113
Vitamin C (mg/day)	124 ± 108
Biochemical indices	
Hematocrit (%)	40.5 ± 2.9
Hemoglobin (g/dl)	12.1 ± 1.0
Plasma iron (µg/dl)	114 ± 50
Plasma zinc (µg/dl)	63 ± 12
Plasma folate (ng/dl)	5.8 ± 2.6
Erythrocyte folate (ng/dl)	157 ± 60
Plasma vitamin C (mg/dl)	1.5 ± 0.2

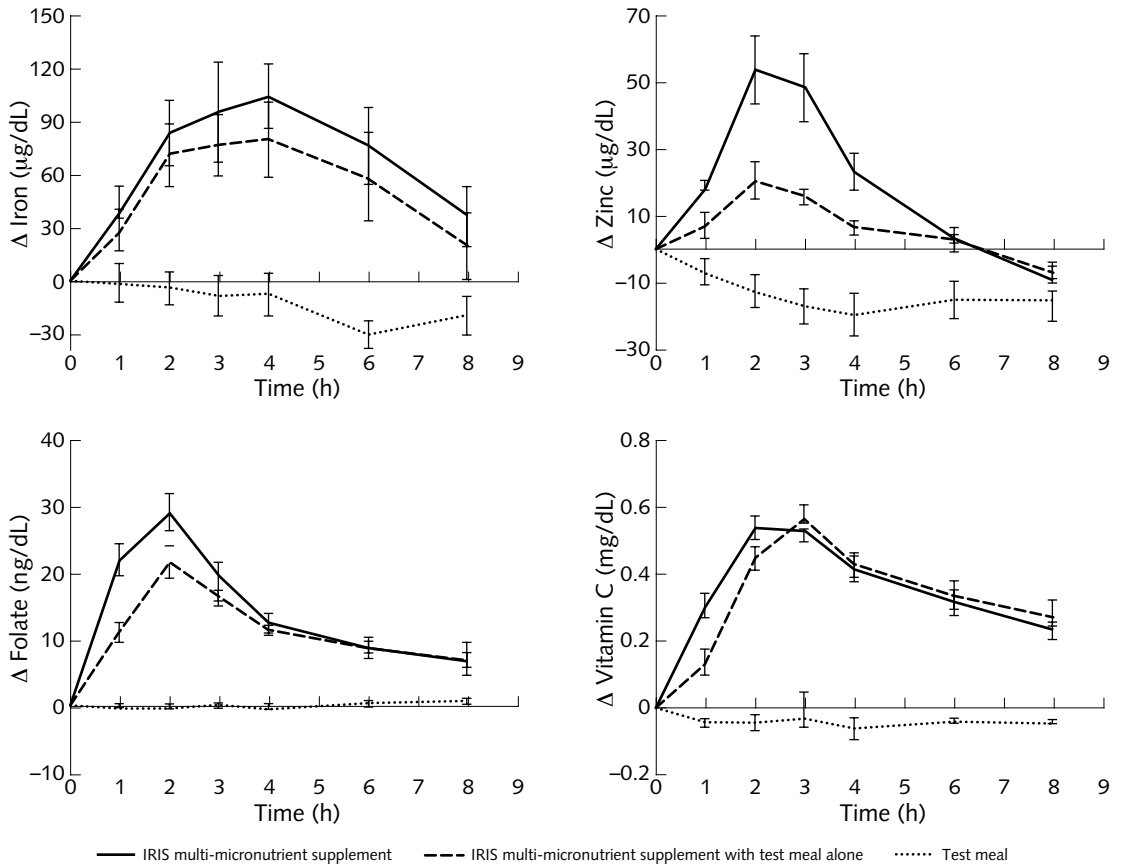


FIG 1. Increments of micronutrient concentrations in plasma over time after each test.
The increment in plasma micronutrient concentration (Δ) at each time point was calculated by the difference between concentration at the corresponding time point and baseline concentration.

TABLE 4. Plasma response of micronutrients to each test

Micronutrient and Test*	Area under the curve (AUC)	Maximum increment in plasma concentration (ΔC_{max})	Time at maximum increment (h)
Iron	(μg/dl × h)	(μg/dl)	
S	550 ± 96	149 ± 23	3.8 ± 0.6
MS	435 ± 125[a]	99 ± 23[a]	3.4 ± 0.5
M	–100 ± 36	—	—
Zinc	(μg/dl × h)	(μg/dl)	
S	150 ± 28	60 ± 10	2.2 ± 0.2
MS	54 ± 14[c]	30 ± 4.5[b]	2.2 ± 0.2
M	–111 ± 32	—	—
Folate	(ng/ml × h)	(ng/ml)	
S	105 ± 8	28 ± 2	1.8 ± 0.1
MS	91 ± 6[a]	22 ± 2[c]	2.1 ± 0.1
M	0.02 ± 1.1	—	—
Vitamin C	(mg/dl × h)	(mg/dl)	
S	2.90 ± 0.22	0.56 ± 0.03	2.5 ± 0.2
MS	3.06 ± 0.30	0.56 ± 0.03	2.7 ± 0.1
M	–0.30 ± 1.9	—	—

Results expressed as mean ± SE.
Significantly different from treatment S: [a] $p<0.05$; [b] $p<0.02$; [c] $p<0.01$
* Tests: S, IRIS multi-micronutrient supplement; MS, IRIS multi-micronutrient supplement with test meal; M, Test meal

plasma concentrations for all the micronutrients was not significantly different between MS and S.

Relative bioavailability (figure 2) was significantly reduced from 100% for iron (80%), zinc (70%), and folate (85%), but not for vitamin C, when the multi-micronutrient supplement was combined with the test meal.

Discussion

Multi-micronutrient supplementation is effective in treating multiple micronutrient deficiencies in infants [15]. However, micronutrient bioavailability can be affected by the use of food as a vehicle of supplementation. Dietary components can enhance or inhibit micronutrient absorption through interactions between the micronutrients from the tablet and the components present in the food matrix [8].

The cornstarch porridge tested in this study is a common weaning food in Brazil. It is a low-cost food and an adequate matrix for dispersion of multi-micronutrient supplement particles. It contains no phytic acid, which has a strong inhibitory effect on mineral bioavailability [8]. Moreover, it contributes to calcium and protein intake. It has been recommended that complementary foods contribute about half of the calcium requirements of infants aged 6 to 24 months [16]. Because IRIS multi-micronutrient supplement contains only small amounts of calcium (in order to contribute to the stability of the tablet), the cornstarch porridge can be viewed as a source of calcium for the infant.

Our study showed that combining the multi-micronutrient supplement with cornstarch porridge did not affect the bioavailability of vitamin C, but reduced the bioavailability of folate, iron, and zinc. Among the studied micronutrients, vitamins were less affected than were minerals. The plasma increment responses of vitamin C to the multi-micronutrient supplement alone or in combination with the cornstarch porridge observed in our study were comparable to those observed in a study of healthy individuals using commercial forms of synthetic vitamin C [17]. Because it is efficiently absorbed in humans, vitamin C bioavailability is generally high—usually 80% to 98% from mixed diets—with little effect of the food matrix [8].

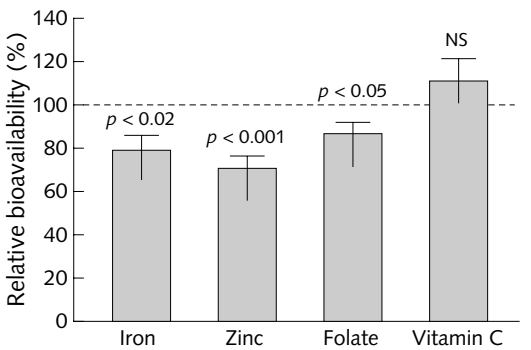


FIG 2. Relative bioavailability of micronutrients in the IRIS multi-micronutrient supplement combined with the test meal. The relative bioavailability of each micronutrient was determined from the ratio between AUC of MS corrected by M and the AUC of S, expressed as a percentage.

The present study showed that when multi-micronutrient supplements were given in combination with the test meal, the AUC of folate was significantly smaller ($p < 0.05$) than it was in absence of food, resulting in a 15% decrease in its relative bioavailability. This may be explained by a slower diffusion rate through the "unstirred water layer" of the intestinal mucosa due to non-digestible viscous components of the cornstarch [18]. A study on absorption of supplemental folate consumed with or without a light breakfast meal [19] showed a 15% reduction in folate bioavailability when folate was given with the meal.

The bioavailability of zinc and of iron were affected more so than that of folate when the IRIS supplement was combined with porridge. The bioavailability of these nutrients from foods with added minerals is generally much lower than it is from pure chemical compounds given in aqueous solutions. In human studies, zinc absorption from pure salts in aqueous solution was about 70%, whereas zinc absorption from foods with zinc added to the same amount was about 20% [20]. Similarly, iron absorption from ferrous sulfate was about 35% when given in aqueous solution and about 5% when given mixed with bovine milk [21].

The reduction in the relative bioavailability of zinc and iron observed in the present study may be due to interactions with components in the meal. Although the porridge did not contain phytate, it contained tannins from the cinnamon used to flavor the porridge. Tannins are major constituents of cinnamon [22] and they can form insoluble complexes with divalent metal ions, thus reducing absorption [23]. In a study of iron absorption from porridges fortified with iron salts, a reduction of 24% in iron absorption was attributed to the tannins in cinnamon added to the porridge [24].

Casein from whole milk may also have contributed to reduced iron and zinc bioavailability, because partially undigested casein subunits may bind these elements and reduce intestinal absorption [25]. Zinc absorption from whey-predominant formula in human adults was higher than from casein-predominant formulas (32% versus 21%) [26]. Poor bioavailability of iron in infant formulas has been attributed at least in part to casein and whey proteins from bovine milk [27].

The calcium in the porridge may have contributed to reduced iron bioavailability. Single-meal human absorption studies have shown that calcium impairs iron absorption, both when given as supplements and

when consumed from dairy products [28]. The inhibitory effect of calcium on iron absorption is independent of the concentrations of phytate or ascorbic acid in a meal [29]. However, the inhibitory effect of calcium on zinc absorption depends on the simultaneous presence of phytate [25]. Therefore, in the present study it is unlikely that calcium had a negative effect on zinc relative bioavailability, because the test meal did not contain phytate.

Although this study was conducted in adult women, the results obtained can be considered a useful guide for young children. After 6 months of age, infants reach a satisfactory gastrointestinal absorptive capacity and become physiologically qualified to adapt to different foods [30]. Moreover, dietary factors that affect nutrient bioavailability do not differ between adults and young children [31]. The observed decrease in bioavailability of folate, iron, and zinc when the IRIS multi-micronutrient supplement was combined with a milk-based cornstarch porridge was relatively small. Therefore, the test food used in this study is a suitable vehicle for the IRIS multi-micronutrient supplement.

Acknowledgements

The authors thank Dr. Carmen Lucia Porto da Silveira of Pontifica Universidade Católica (Rio de Janeiro, Brazil) for her assistance with ICP-AES facilities, and the participating women for their motivation and cooperation. Financial support from CNPq, FAPERJ, and FUJB (Brazil) is also acknowledged. Authors Donangelo, Trugo, and Kamp are recipients of CNPq fellowships.

References

1. WHO/UNICEF/UNU. Consultation on iron deficiency: indicators and strategies for iron deficiency control programmes. Geneva: World Health Organization, 1992.
2. Allen LN, Rosado JL, Casterline JE, López P, Muñoz E, Garcia OP, Martinez H. Lack of hemoglobin response to iron supplementation in anemic Mexican preschoolers with multiple micronutrient deficiencies. Am J Clin Nutr 2000;71:1458–94.
3. Prasad AS. Zinc deficiency in human: a neglected problem. J Am Coll Nutr 1998;17:542–3.
4. Herbert V. Folic acid. In: Shils ME, Olson JA, Shike M, Ross AC, eds. Modern nutrition in health and disease. Baltimore, MD: Williams & Wilkins,1999;433–46.
5. Jacob RA. Vitamin C. In: Shils ME, Olson JA, Shike M, Ross AC, eds. Modern nutrition in health and disease. Baltimore, MD: Williams & Wilkins, 1999;467–83.
6. UNICEF/WHO/UNU. Composition of a multi-micronutrient supplement to be used in pilot programs among pregnant women in developing countries. New York: UNICEF, 1999.
7. Gross R. Micronutrient supplementation throughout the life cycle. New York: UNICEF, 1999.
8. Fairweather-Tait S. Bioavailability: definition and general aspects. In: Sadler MJ, Strain JJ, Caballero B, eds. Encyclopedia of human nutrition. London, UK: Academic Press, 1999;164–70.
9. Schaffert RR, Kingsley GR. A rapid, simple method for the determination of reduced, dehidro and total ascorbic acid in biological materials. J Biol Chem 1955;212: 59–68.
10. Pfeifer S, Pflegel P, Borchert HH. Grundlagen der Biopharmazie: Pharmakokinetik, Bioverfügbarkeit, Biotransformation (Fundamentals of biopharmacy: pharmacokinetics, bioavailability, biotransformation). Weinheim, Germany: Verlag-Chemie, 1984.
11. Institute of Medicine. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press, 2001.
12. Alcock NW. Laboratory tests for assessing nutritional status. In: Shils ME, Olson JA, Shike M, Ross AC, eds. Modern nutrition in health and disease. Baltimore, MD: Williams & Wilkins, 1999;923–35.
13. Wallock LM, King JC, Hambidge KM, English-Westcott JE, Pritts J. Meal-induced changes in plasma, erythrocyte, and urinary zinc concentrations in adult women. Am J Clin Nutr 1993;58:695–703.
14. Cousins RJ. Absorption, transport, and hepatic metabolism of copper and zinc: special reference to metallothionein and ceruloplasmin. Physiol Rev 1985;65: 238–309.
15. Rivera JA, González-Cossio T, Flores M, Romero M, Rivera M, Téllez-Rojo MM, Rosado JL, Brown KH. Multiple micronutrient supplementation increases the growth of Mexican infants. Am J Clin Nutr 2001;74: 657–63.
16. Brown KH, Dewey KG, Allen LH. Complementary feeding of young children in developing countries: a review of current scientific information. Geneva: World Health Organization, 1997.
17. Johnston CS, Luo B. Comparison of the absorption and excretion of three commercially available sources of vitamin C. J Am Diet Assoc 1994;94:779–81.
18. Gallaher DD, Schneeman BO. Dietary fiber. In: Ziegler EE, Filer LJ, eds. Present knowledge in nutrition. Washington, DC: ILSI Press, 1996;98–108.
19. Pfeiffer CM, Rogers LM, Bailey LB, Gregory JF 3rd. Absorption of folate from fortified cereal-grain products and of supplemental folate consumed with or without food determined by using a dual-label stable-isotope protocol. Am J Clin Nutr 1997;66:1388–97.
20. Sandström B, Davidsson L, Cederblad Å, Lönnerdal B. Oral iron, dietary ligands and zinc absorption. J Nutr 1985;115:411–4.
21. Stekel A, Amar M, Calvo E, Chavud P, Hertrampf E, Lla-

guno S, Olivares M, Pizarro F. Nutritional significance of interactions between iron and food components. Arch Latinonoam Nutr 1983;33:33–41.
22. Hamano T, Yasuda I, Haeneishi N, Takano I, Seto T, Nishijima M. Evaluation of cinnamon barks on the market. Nat Med 1996;50:384–8.
23. Tuntawiroon M, Sritongkul N, Brune M, Rossander-Hulten L, Pleehachinda R, Suwanik R, Hallberg L. Dose-dependent inhibitory effect of phenolic compounds in foods on nonheme-iron absorption in men. Am J Clin Nutr 1991;53:554–7.
24. Mendoza C, Viteri FE, Lönnerdal B, Raboy V, Young KA, Brown KH. Absorption of iron from unmodified maize and genetically altered, low-phytate maize fortified with ferrous sulfate or sodium iron EDTA. Am J Clin Nutr 2001;73:80–5.
25. Lönnerdal B. Dietary factors influencing zinc absorption. J Nutr 2000;130:1378S–83S.
26. Lönnerdal B, Cederblad A, Davidsson L, Sandström B. The effect of individual components of soy formula and cow's milk formula on zinc bioavailability. Am J Clin Nutr 1984;40:1064-70.
27. Hurrell RF, Lynch SR, Trinidad TP, Dassenko SA, Cook JD. Iron absorption in humans as influenced by bovine milk proteins. Am J Clin Nutr 1989;49:546–52.
28. Lynch SR. The effect of calcium on iron absorption. Nutr Res Rev 2000;13:141–58.
29. Hallberg L, Rossander-Hultén, Brune M, Gleerup A. Calcium and iron absorption: mechanism of action and nutritional importance. Eur J Clin Nutr 1992;46:317–27.
30. Pipes PL. Infant feeding and nutrition. In: Pipes PL, Trahms CM, eds. Nutrition in infancy and childhood. St. Louis: Mosby, 1993;87–117.
31. Krebs NF. Bioavailability of dietary supplements and impact of physiologic state: infants, children and adolescents. J Nutr 2001;131:1351S–4S.

IRIS I: A FOODlet-based multiple-micronutrient intervention in 6- to 12-month-old infants at high risk of micronutrient malnutrition in four contrasting populations: Description of a multicenter field trial

International Research on Infant Supplementation (IRIS I) Study Group:
C. Marius Smuts, A.J. Spinnler Benadé, Jacques Berger, Le Thi Hop, Guillermo López de Romaña, Juliawati Untoro, Elvina Karyadi, Jürgen Erhardt, and Rainer Gross

Editors' Note

The overall plan for execution of IRIS originated in the 1999 workshop in Rio de Janeiro; that meeting produced an overall scope and approach to intervention later refined into a multicenter protocol. It took the work of a number of professionals around the world and analyses of biochemical samples and tabulated data to bring us a preliminary look at the experience and findings from the actual IRIS study to the plenary discussions at the Lima gathering. Only a short interval had elapsed between the conclusion of work in the field and laboratories and the convening of the workshop. The broad authorship of this paper recognizes the full array of participants in IRIS I activity. The results and findings presented by the teams in Lima were in a preliminary state of analysis, had not been subjected to combined across-site analysis, and have yet to be fully analyzed for publication. However, the plenary sessions provided an inventory of just how close (or how far) to the intended procedural mark were the specific individual trials in Peru, South Africa, Vietnam, and Indonesia. This paper presents this inventory and draws out the valuable lessons learned for the general practice of multinational common-protocol field investigation.

C. Marius Smuts and A.J. Spinnler Benadé are affiliated with the Nutritional Intervention Research Unit, MRC, in Parow, South Africa; Jacques Berger is affiliated with the Institute of Research for Development (IRD) in Hanoi, Vietnam; Le Thi Hop is affiliated with the National Institute of Nutrition in Hanoi, Vietnam; Guillermo López de Romaña is affiliated with the Instituto de Investigación Nutricional in Lima, Peru; Juliawati Untoro and Elvina Karyadi are affiliated with the SEAMED-TROPMED Regional Center for Community Nutrition at the University of Jakarta in Jakarta, Indonesia; Jürgen Erhardt is affiliated with the Institute of Biological Chemistry and Nutrition at the University of Hohenheim in Stuttgart, Germany; and Rainer Gross is affiliated with UNICEF in New York City, USA. Address for correspondence: Dr CM Smuts, PO Box 19070, Tygerberg 7505, Cape Town, South Africa; email: marius.smuts@mrc.ac.za.

Abstract

Infants in developing countries are at risk of concurrent micronutrient deficiencies, because the same causative factors may lead to deficiencies of different micronutrients. Inadequate dietary intake is considered one of the major causes of micronutrient deficiencies, especially among poor and underprivileged children in developing countries. Operational strategies and distribution systems are often duplicated when supplementation programs for single micronutrients are implemented at the same time. The International Research on Infant Supplementation (IRIS) trial was conducted in four distinct populations on three continents: Africa, Latin America, and Asia. The participating countries were South Africa, Peru, Vietnam, and Indonesia. The study had a randomized, double-blind, placebo-controlled design. Each country aimed to enroll at least 70 infants per intervention group (65 + 5 anticipated dropouts). The micronutrient vehicle was in the form of a "foodlet" (food-like tablet) manufactured as chewable tablets, which were easy to break and dissolve, and which had the same taste, color, and flavor for all countries.

Children were randomly assigned to one of four 6-month intervention groups: group 1 received a daily foodlet containing multiple micronutrients; group 2 received a daily placebo foodlet containing no micronutrients; group 3 received a weekly foodlet that contained multiple micronutrients (twice the dose of the daily foodlet) and placebo foodlets on the other days of the week; group 4 received a daily foodlet containing only 10 mg of elemental iron.

The IRIS Trial aimed to examine the prevalence of multi-micronutrient deficiencies in 6- to 12-month-old infants from rural populations, and to examine the efficacy of multi-micronutrient supplementation in infants from the different countries included in the study. This paper describes the general methodology of the IRIS trial and the operational differences among the country sites.

Key words: developing countries, foodlet, infants, multicenter trial, multi-micronutrient supplements, supplementation

Introduction

In the developing world, many vulnerable population groups suffer from multiple nutrient deficiencies. Of these deficiencies, iron, vitamin A, and iodine are the most commonly reported, although there may also be deficiencies of other vitamins and minerals. Infants are likely to have multiple, concurrent deficiencies, because the same causative factors may lead to a deficiency of different micronutrients. Cereal-based diets, rich in phytate and low in animal products, which predispose people to insufficient absorption of both iron and zinc, are commonly consumed in developing countries [1]. Micronutrient deficiencies are of global importance, as exemplified by several nutrition goals set in the early 1990s, including the virtual elimination of vitamin A and iodine deficiency, the reduction of iron-deficiency anemia in women by one-third, and the halving of severe and moderate undernutrition in children under 5 years of age by the year 2000. Although there have been considerable advances toward achieving these goals, a realignment of some goals adopted at the United Nations General Assembly Special Session on Children, May 2002, has been necessary due to challenges in research and implementation. The revised goals include reducing the percentage of children under the age of 2 with stunted growth by at least one-third, establishing sustained elimination of iodine deficiency disorders by 2005, and reducing the prevalence of anemia, including iron-deficiency anemia, in pregnant women and infants younger than 2 by at least one-third of the 2000 level by the year 2010.

Adequate intake of iron, vitamin A, zinc, and iodine is essential for growth and mental and motor development, and for the prevention of disease. Children with micronutrient deficiencies often present with linear growth retardation, higher morbidity and mortality, and reduced psychomotor development, preventing them from developing to their full potential [2, 3]. Exclusive breast-feeding during the first 6 months of life is considered sufficient to provide adequate nutrition for infants [4]. The transition to complementary foods in the process of weaning children to household diets, however, is associated with risks of nutrient deficiencies [5], due to the low density and/or poor bioavailability of certain nutrients in some household diets. It is well known that anemia is common in infants even in industrialized nations [6, 7], and that obtaining sufficient zinc from dietary sources is a challenge in most settings [5]. The consequence may be widespread prevalence of deficiencies of iron, zinc, and other assorted micronutrients from 7 months of age onward, especially in low-income societies [8, 9]. Providing for optimal nutrition status of infants born under the least favorable socioeconomic and climatic conditions would require exclusive breast-feeding during the first 6 months of life, with the possible application of routine dietary enrichment with selected micronutrients during the period of weaning transition [10].

It is theoretically possible that the currently recommended daily intakes of nutrients for infants, based on the US recommended dietary allowances (RDAs) (part of the *Dietary Reference Intakes*, or DRIs) [11], for instance, are not yet refined to genuine suitability. Or, they may indeed be correct for infants in the industrialized settings in which they are derived, but are not applicable to situations in which the majority of the populace is not "healthy," as defined in the disclaimers for application of the RDAs [11, 12]. The environmental stresses of extreme climate, parasites, poor sanitation, and recurrent infections may contribute to higher demands or a greater loss of nutrients; alternatively, the slower growth of infants may produce an imbalance between an abundant micronutrient offering and lowered total body demands. However, for the context of prophylaxis and support of micronutrient nutriture for an infant population, the dosages of published recommended levels would seem a reasonable and prudent point of departure [10].

The International Research on Infant Supplementation (IRIS) initiative arose in the context of the aforementioned public health questions [10]. It realized that before generalization of any supplementation of micronutrients at the programmatic level (even at the prudent dosages of approximately 1 RDA) could be justified, any issue regarding its efficacy and safety would have to be resolved. For the purposes of a robust initial evaluation, the IRIS group opted for a multicenter approach, in which the diverse ethnic and environmental context of three low-income regions—Latin America, Africa, and Asia—would be included, and the study populations would be subjected to a common intervention protocol, with the inclusion for reference of a no-treatment (placebo) control. The micronutrient vehicle would be an innovative feature, in the form of a "foodlet" (food-like tablet), conceived in consultation with international experts in Rio de Janeiro [10].

The primary format for supplementation administered essential micronutrients, dosed at infant RDA levels, every day for 6 months. Combining multiple micronutrients in a single delivery mechanism has been suggested as a cost-effective way to achieve multiple benefits [13, 14]. Some have questioned the effectiveness of nutrients combined within a supplement because of possible interactions of the nutrients or interference in their absorption [15, 16]. Given the specific recalcitrance of redressing iron nutrition problems at the public health level, a daily iron-only

treatment group was added to identify any potential factors of nutrient-nutrient interactions related to iron in combination with other vitamins and minerals. Finally, because of data showing that intermittent (e.g., weekly) micronutrient supplementation could be less expensive and easier for participants to follow [17], a weekly (compared with daily) supplement was a final feature of the four-arm, randomized design.

Thus, a protocol was developed to explore the efficacy of multi-micronutrient supplementation in infants from micronutrient-deficient populations on three continents. After verification and inputs from the various participating countries, namely, Indonesia, Vietnam, Peru, and South Africa, the objectives of the study were as follows: (1) to examine the prevalence of multi-micronutrient deficiencies in infants from rural populations of these four selected countries; and (2) to assess the efficacy of multi-micronutrient supplementation in these infants on three parameters: the selected micronutrient status, anthropometric status, and morbidity status. This paper describes the general methodology of the IRIS trial and the operational differences between the country sites.

Populations, subjects, materials, and methods

Populations

Four geographically distinct populations from three continents participated in the study. The participating countries were South Africa, Peru, Vietnam, and Indonesia. Settings with a historical prevalence of anemia (defined as hemoglobin < 110 g/L) and vitamin A deficiency (< 0.7 μmol/L), ranging up to 30% of the preschool (under 5 years of age) population, were selected for an inquiry into the nutrition status of infants during their second semester of life.

In South Africa, the study was carried out in the geographic area of the Valley of a Thousand Hills, situated approximately 40 km northwest of the coastal city of Durban in the KwaZulu-Natal Province. This is a rural region in which families are scattered over a very large mountainous area. The community is predominantly Zulu. In Peru, the study was carried out in peri-urban communities of two cities of the department of Lambayeque (Lambayeque and Chiclayo), located approximately 600 km north of Lima, the capital of Peru. In Vietnam, the study was conducted in four communes (Phu Minh, Duc Hoa, Xuan Thu, and Phu Lo) in the rural district of Socson, 50 km North of Hanoi City. The Indonesian study was conducted in two subdistricts of Salam and Ngluwar, district of Magelang, province of central Java, Indonesia.

For ethical considerations the guidelines of the Council of International Organizations of Medical Sciences [18] were followed. Before the study, mothers were informed about the purpose and different phases of the study. The ethical review committees of each of the institutions approved the protocols and planned procedures and supervised the protection of autonomy and exclusion of undue risk for the participants. Parents or legal guardians of each participating child gave witnessed, informed (written) consent.

Selection of subjects

Within the populations, various randomization strategies were used to pre-select children for potential inclusion from the infant population of the given community. Eligibility for enrollment was determined by inclusion criteria that included being a stable resident of the catchment's area of interest, being of either sex, and having more than 180 and less than 365 days of age for the moment of initial measuring and sampling. Exclusion criteria for non-eligibility included failure to obtain signed informed consent, premature birth (< 37 weeks gestation), low birth weight (< 2500 g), severe wasting (< 3 Z-scores), anemia (hemoglobin < 80 g/L), and fever (> 39°C) on the day of blood sampling.

Study design and enrollment process

The study had a randomized, double-blind, placebo-controlled design. Children were randomly assigned to one of four intervention groups. Through the use of coding, the subjects' families as well as the investigators were blinded to the specific composition of the foodlets assigned. If a family had more than one child who was eligible to participate in the study, they were treated as separate cases, but were allocated to the same intervention group. Each country received a simple computer program to use in their randomization process. The sample size was calculated based on a power index of 2.86 and an anticipated dropout of about 7%. Thus, each country aimed to enroll at least 70 infants per intervention group (65 + 5 dropouts).

All subjects participated for 6 months. Group 1 received a daily foodlet containing multiple micronutrients. Group 2 received a daily placebo foodlet containing no micronutrients. Group 3 received a weekly foodlet containing multi-micronutrients at twice the dose of the daily foodlet and placebo foodlets on the other days of the week. Group 4 was given a daily foodlet containing 10 mg of elemental iron.

The RDA multi-micronutrient (MM) foodlet (daily dose) contained 1 RDA micronutrients for children aged 1 to 2 years, with the exception of zinc, which was the equivalent of 1 RDA for children aged 6 to 12 months. The weekly 2 RDA MM foodlet was equivalent to twice the daily dose. All foodlets had a piña colada flavor to make them acceptable to infants. The placebo foodlet contained no micronutrients. A week's supply

was distributed in coded blister packs. Ingredients and dosing for the 1 RDA supplement are presented in table 1.

Roche Laboratories (New York, USA) was responsible for the elaboration of the final blend of the product, and a private laboratory in Peru (Hersil SA, Peru) was responsible for the production and quality control of the supplements. Foodlets were manufactured as chewable tablets, which were easy to break and dissolve, and which had the same taste, color, and flavor for all countries. Three of the groups (placebo, iron, and daily multi-micronutrients) had blisters with seven tablets and within each group all tablets had the same composition; the fourth group (weekly multi-micronutrients) had blisters that included six placebo tablets and one 2 RDA tablet placed always in the same position within the blister arrangement. For all intervention groups, the first foodlet used from a blister was from this position. Before the final production, a double-blind acceptability trial was carried out in the study area of Peru with the participation of 50 infants and their mothers. Results showed that there was good acceptability of the four presentations. The other countries also found the foodlets very acceptable by their respective target populations. Coded blisters were distributed to all participating countries. Codes were kept by UNICEF, New York, and only broken at the end of the study, prior to statistical analyses.

Consumption of foodlets

In Indonesia and Peru, the foodlets were administered to the babies at home on a daily basis for 7 days. On six of the days, a trained field worker/assistant gave the foodlets directly to the babies and on the seventh day the mother gave the supplement to the infant. Compliance with the administration of the first six supplements to the infants was recorded directly, and that of the seventh during the next day's visit. In Vietnam, the foodlets were given daily to the infants under close supervision of the commune health workers, who recorded compliance. In South Africa, all blisters and working materials were color-coded to facilitate and simplify the identification of groups. Mothers were provided with one month's foodlet supply in a color-coded container, because the study was done in a rural, scattered area and it was impossible for community health workers to visit all households on a daily basis. The mothers and/or caregivers were given demonstrations on how to how to crumble and mix the foodlet with porridge. Mothers were trained to mix foodlets with a small quantity of porridge (maize meal predominantly), as it was important that the child should eat the entire portion mixed. Compliance was monitored during weekly visits by the community health workers by means of a short questionnaire and observation (the number of foodlets removed from the previous week's blister was counted and recorded).

TABLE 1. Composition of 1 RDA multi-micronutrient foodlet.

Ingredients	Amount	Product form	% overage	mg per foodlet
Vitamin A	375 µg RE (1250 IU)	A acetate 325 CWS/F	35	5.2
Vitamin D	5 µg	D 100 CWS	35	2.7
Vitamin E	6 mg α-TE	E 50 CWS/F	10	13.2
Vitamin K	10 µg	0.5% Trit	50	3
Vitamin C	35 mg	Fine C powder	5	36.75
Vitamin B_1	0.5 mg	Rocoat 33 1/3%	10	1.65
Vitamin B_2	0.5 mg	Rocoat 33 1/3%	10	1.65
Vitamin B_6	0.5 mg	Rocoat 33 1/3%	7.5	1.61
Vitamin B_{12}	0.9 µg	0.1% WS	30	1.17
Niacin	6 mg	Niacinamide	5	6.3
Folate	150 µg	10% triturated	25	1.88
Iron	10 mg	Ferrous fumarate (32.87% Fe)		30.42
Zinc	5 mg	Zinc gluconate (14.35% Zn)		34.84
Copper	0.6 mg	Cupric gluconate (14% Cu)		4.3
Iodine	59 µg	1% potassium iodide trit		5
Milk solids				1,100
DiPac		Piña colada		600
6X Sugar		Calcium carbonate 90 A		600
Fructose				240
Flavor				52.4
Citric acid				22.4
Calcium carbonate				53
Magnesium stearate				13.5
		Supplement weight (mg)		2,830.97

Questionnaires

All information was collected in a closed questionnaire according to the recommendations of Gross et al. [19] (http://www.nutrisurvey.de). The questionnaire comprised four different components, namely, (1) the baseline or household questionnaire, which was only used at the beginning of the trials; (2) the monthly weight and height questionnaire, which also included the date of measurement to calculate with the age of the child the Z-scores; (3) the weekly health visit form; and (4) the daily health and infant feeding information questionnaire. All daily information obtained was converted to weekly information.

Anthropometry and assessment of growth

Infants' anthropometric measurements were measured on a monthly basis. Length was measured with the subject supine, using an infantometer measuring board (Ahrtag, London, UK), and recorded to the nearest 0.1 cm. Weight was determined with minimal clothing on electronic weighing scales (SECA, Hamburg, Germany). In South Africa, weight was measured to the nearest 50 grams on a load-cell-operated digital scale (UC-300 Precision Health Scale). All anthropometric measurements were taken by the same person in South Africa to minimize individual variation; similarly, in Vietnam, the same two people measured height and weight separately.

Blood collection and sample processing and handling

Blood was obtained from the vein with 2 ml–vacuette heparin tubes with butterfly luer-lock adapters (Greiner, Essen, Germany). The puncture site was cleaned carefully with cotton wool and 70% alcohol. After collection, tubes were immediately put in a cooled styropore box with coolpacks and centrifuged within 6 hours at 5000 g for 5 minutes. Plasma and erythrocytes were stored at –70°C until transportation on dry ice to Germany where they were analyzed in the Micronutrient Laboratory of the Institute of Biological Chemistry and Nutrition at the University of Hohenheim (the exceptions were hemoglobin and urinary iodine, which were measured at each site). All materials used for blood taking and storage were from the same batch and provided by the biochemical laboratory in Germany.

Hematologic assessment

Hemoglobin concentrations were determined with the cyanomethemoglobin method [20] by using a kit from Sigma (Sigma, St. Louis, USA); 20 µl whole blood were mixed with 5 ml Drabkins solution and measured by a standard photometer and quantified with a Hb standard. All populations were located within 500 meters of sea level, such that no altitude adjustment was needed.

Biomarkers of mineral nutriture

Serum ferritin was measured by a standard sandwich ELISA procedure from the provider of the antibodies (DAKO, Hamburg, Germany). Plasma zinc and copper concentrations were analyzed by flame atomic absorption spectrophotometry according to the description of the manufacturer (Perkin Elmer, Frankfurt, Germany). Urinary iodine concentrations were assessed based on alkaline digesting using the Sandell-Kolthoff reaction [21].

Biomarkers of vitamin nutriture

Retinol, α-tocopherol, and β-carotene were analyzed according to Erhardt et al. [22]. The plasma proteins were denatured by mixing 30 µl plasma with 150 µl ethanol/n-butanol (1:1 v/v, containing 5 mg BHT/ml and 4 µmol/l Tocol as internal standard). The mixture was then centrifuged for 5 minutes at 12,000 g and 30 µl of the supernatant were analyzed by using reversed phase high-performance liquid chromatography (HPLC). For homocysteine as an indicator of folic acid status, the HPLC method of Pfeiffer et al. [23] was used. Homocysteine status is also influenced by vitamin B_6 and vitamin B_{12}. For the riboflavin status, the method of Bayoumi and Rosalki [24] was used by calculating the activation coefficient of the erythrocyte glutathione reductase with and without added riboflavin.

Biomarkers of activation of the acute-phase response

Infectious status was measured by C-reactive protein (CRP) for short-term effects and by α-1-acid glycoprotein (AGP) for long-term effects. For these measurements, a Sandwich ELISA was used according to the description of the manufacturer of the antibodies (DAKO, Hamburg, Germany). Elevation for CRP was considered to be a value of > 12 mg/L, whereas abnormally high AGP was a concentration of > 1 g/L. The status of an abnormally increased acute-phase-response marker was taken into consideration for the diagnostic assessment and interpretation of retinol, zinc, and iron status markers. Table 2 presents a summary of anthropometric measurements and all biochemical analyses done on blood samples, as well as the time of measurement.

Data processing and statistical analysis

All collected data were entered into a spreadsheet using SPSS. The Medical Research Council, South Africa, will carry out the statistical evaluation of the data collected at all sites.

TABLE 2. Anthropometric and biochemical variable indicator matrix and time of measurement.

Variable	Indicators	Time of Measurement
Anthropometry	Weight	Monthly
	Height	Monthly
Morbidity	Diarrhea, acute respiratory infection, fever	Daily*
Iron status	Hemoglobin	Begin/end
	Plasma ferritin	Begin/end
Vitamin A status	Plasma retinol	Begin/end
	Plasma β-carotene	Begin/end
Vitamin B status	Plasma homocysteine	Begin/end
	Plasma riboflavin	Begin/end
Vitamin E status	Plasma α-tocopherol	Begin/end
Zinc status	Plasma zinc	Begin/end
Copper status	Plasma copper	Begin/end
Iodine status	Urinary iodine excretion	Begin/end
	Iodine content in the household salt	At least begin/end
Acute phase proteins	C-reactive protein	Begin/end
	α-1-acid glycoprotein	Begin/end

* On a weekly basis in South Africa.

Discussion

At the International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle in Lima, Peru (May 30–June 1, 2001), it was indicated that the question of efficacy and safety of multiple micronutrient supplementation must be addressed before programs can be devised and implemented [25]. The IRIS trial should provide concrete evidence of efficacy of multi-micronutrient supplementation in infants with a diverse background from three continents, and some evidence of safety. The "foodlet" concept was conceived at the Rio de Janeiro meeting to have multiple attributes [10]. Firstly, the intention was to move nutrient supplementation out of the medicinal form and dominant health-sector-control arena and into a dietary and food context. This accepts that matrix factors might reduce the net bioavailability as compared with that in a capsule or elixir, but this would be an acceptable tradeoff if compliance were enhanced proportionately. The foodlet was conceived of to be a crumbly, cookie-like item, a "tabletted snack" that could be either sucked to dissolution by edentulous infants, or gnawed or chewed by babies with teeth, or crumbled and sprinkled onto a porridge or pap, or mixed into gruels or beverages. Each country was allowed to administer the foodlets to infants by means of an acceptable practice for that specific community. Inter-mealtime consumption with a high compliance was managed in three of the sites. In Vietnam, for instance, the foodlet was dissolved in a little water in a cup and given with a spoon to the infant. In South Africa, the foodlet was crushed and mixed into the traditional maize gruel as the introduction of weaning food that usually begins during early infancy there. Nevertheless, compliance was good and estimated to be well above 90%.

The intervention period was 6 months for all participating countries, except for Indonesia, where the period fell one week short due to a big Moslem festival of *Iedul Fitri*, which was celebrated by the majority of study subjects. Research activity in the community during that period was not recommended. Further, all countries followed the protocol closely, taking into account their own unique situations and circumstances. The only deviation occurred in South Africa, where infants did not take the supplement under close supervision of study workers due to the rural geographic area where the study subjects were scattered. Therefore all compliance and morbidity data were only collected on a weekly basis there. Thus, the South African leg of the study was not executed as a typical efficacy trial in which supplements are taken under close supervision, but more in a deep "rural efficacy" style where mothers and caregivers are trained and empowered to play the supervision role. The South African study can therefore be seen as a hybrid between an efficacy and an effectiveness trial that should provide specific information on how to do efficacy trials in deep rural areas under remote conditions, where the most vulnerable populations for micronutrient deficiency often reside.

A strong point of the IRIS trial was that the biochemical analyses were done centrally at one laboratory, which also provided all material for blood sampling. The laboratory uses micromethods (< 30 μl for each measurement) to reduce the necessary volume of blood as much as possible. Further, it also measures a wide spectrum of indicators including metabolic variables, such as homocysteine.

Conclusion

In conclusion, the outcome of the IRIS I trial should yield unique information on how effectively combined multiple micronutrients can combat micronutrient deficiencies during the second semester of infancy, taking into account the possible interactions and interference in their absorption. This will all be gauged against the consequences that multi-micronutrient supplementation might have on anthropometric and morbidity indicators, using no supplementation or iron-only supplementation as a reference.

Acknowledgements

This study was funded by UNICEF, New York, USA. We would like to thank Dr. Werner Schultink for his support and valuable inputs to this study. Further, we would like to recognize every person who contributed to the success of the IRIS trial. Lastly and most importantly, we wish to recognize the children and mothers who participated in the study.

References

1. Ferguson EL, Gibson RS, Opare-Obisaw C, Ounpuu S, Thompson LU, Lehrfeld J. The zinc nutriture of preschool children living in two African countries. J Nutr 1993;123:1487–96.
2. Kikafunda JK, Walker AF, Collett D, Tumwine JK. Risk factors for early childhood malnutrition in Uganda. Pediatrics 1998;102:E45.
3. Vazir S, Naidu AN, Vidyasagar P. Nutritional status, psychosocial development and the home environment of Indian rural children. Indian Pediatr 1998;35:959–66.
4. Baumslag N, Favin M. Do infants under six months of age need extra iron? A probe. Working Paper #12. Arlington, VA: MotherCare, John Snow Inc, 1992.
5. Brown KH, Dewey KG, Allen LH. Complementary feeding of young children in developing countries. New York: UNICEF, 1998.
6. Dallman P, Siimes M. Iron deficiency in infancy and childhood. Washington, DC: The International Nutritional Anemia Consultancy Group, 1979.
7. Yip R. Iron deficiency: Contemporary scientific issues and international programmatic approaches. J Nutr 1994;124:1479S–90S.
8. Ramakrishnan U. Prevalence of micronutrient malnutrition worldwide. Nutr Rev 2002;60:S46–52.
9. Chakravarty I, Sinha RK. Prevalence of micronutrient deficiency based on results obtained from the National Pilot Program on Control of Micronutrient Malnutrition. Nutr Rev 2002;60:S53–8.
10. Gross R. Micronutrient supplementation throughout the life cycle. New York: UNICEF, 2001.
11. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press, 2000.
12. National Research Council, Subcommittee on the 10th Edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences. Recommended Dietary Allowances, 10th Ed. Washington, DC: National Academy Press, 1989.
13. Briend A. Highly nutrient-dense spreads: a new approach to delivering multiple micronutrients to high-risk groups. Br J Nutr 2001; 85 (Suppl 2):S175–S179.
14. Alnwick D. Weekly iodine supplements work. Am J Clin Nutr 1998;67:1103–4.
15. Argiratos V, Samman S. The effect of calcium carbonate and calcium citrate on the absorption of zinc in healthy female subjects. Eur J Clin Nutr 1994;48:198–204.
16. Allen LH. Iron-ascorbic acid and iron-calcium interactions and their relevance in complementary feeding: micronutrient fortification of complementary foods. Washington, DC: International Life Sciences Institute, 1998.
17. Gross R, Angeles-Agdeppa I, Schultink W, Dillon D, Sastromanidjojo S. Daily versus weekly iron supplementation: programmatic and economic implications of Indonesia. Food Nutr Bull 1997;18:64–70.
18. Council for International Organizations of Medical Sciences. International guidelines for ethical review of epidemiological studies. Geneva: CIOMS, 1990.
19. Gross R, Schultink W. Micronutrient deficiency in urban Indonesia. Arch Latinoam Nutr 1997;47(2 Suppl 1): 50–3.
20. International Nutritional Anemia Consultative Group, Nutritional Foundation. Iron deficiency in women. Washington DC: Nutrition Foundation, 1984.
21. Dunn JT, Crutchfield HE, Gutekunst R, Dunn AD. Two simple methods for measuring iodine in urine. Thyroid 1993;3:119–23.
22. Erhardt JG, Mack H, Sobeck U, Biesalski HK. β-Carotene and α-tocopherol concentration and antioxidant status in buccal mucosal cells and plasma after oral supplementation. Br J Nutr 2002;87:471–5.
23. Pfeiffer CM, Huff DL, Gunter EW. Rapid and accurate HPLC assay for plasma total homocysteine and cysteine in a clinical laboratory setting. Clin Chem 1999;45: 290–2.
24. Bayoumi RA, Rosalki SB. Evaluation of methods of coenzyme activation of erythrocyte enzymes for detection of deficiency of vitamins B_1, B_2 and B_6. Clin Chem 1976;22:327–35.
25. Gross R, Dwivedi A, Scrimshaw N. International workshop on multi-micronutrient deficiency control in the life cycle, Lima, Peru, May 30 –June 1, 2001. Food Nutr Bull 2002;23:309–16.

The evolving applications of spreads as a FOODlet for improving the diets of infants and young children

André Briend and Noel W. Solomons

Editors' Note

The multinutrient workshop in this series (convened in 1999 in Rio de Janeiro) focused on the general theses that micronutrient interventions should not be isolated, but combined and provided in a delivery vehicle that approximated a food, in the hope that this might produce a more normal cultural insertion into maternal caring behavior than a more medicinal vehicle. A sweet, chewable tablet-cookie (more tablet than food) had been chosen for IRIS I, and in the intervening two years, food technology and field experience had advanced another potential vehicle. This one is more food-like and with potential advantages for storage and use in humid, tropical environments. This is the nutrient-dense spread, a micronutrient intervention vehicle derived from a product designed originally for rehabilitation of severe protein-energy malnutrition. Investigators close to the development of a fat-based spread for micronutrient intervention introduced those at the Lima workshop to this novel, alternative approach to 'foodlet' technology—all food and no tablet.

Abstract

Action is needed to reduce the burden of micronutrient malnutrition in developing countries, and because low-income populations are vulnerable to deficiencies of multiple micronutrients, we need to move beyond approaches that comprise only single nutrients. The normal and evolutionary manner in which to consume nutrients is in the context of foods, both snacks and meals. Spreads are high-viscosity-fat products prepared by mixing dried powdered ingredients with a vegetable fat chosen for its viscosity. Spreads are not traditionally used for feeding infants or young children and were initially proposed as a way to treat children recovering from severe malnutrition. In preparation for the International Research Group on Infant Supplementation (IRIS) III intervention, a sequel to the IRIS I study (which was the focus of a workshop in Lima, Peru, from May 30–June 1, 2001), the feasibility of preparing a FOODlet for feeding infants and young children was explored. Within the spectrum of intervention tools for micronutrient supplementation, tablets are a pharmaceutical form, fortified spreads are a food, and sprinkles are an intermediate approach. The issues still to be discussed and resolved with regard to creating such a spread include its specific micronutrient formulation, the capacity of young children to consume the required amounts (from either the FOODlet alone or the FOODlet mixed with other foods), the iron content and overall antioxidant protection of the spread matrix and its vitamins, potential allergenicity of proteins, and the economic implications of using such a FOODlet in low-income societies.

Key words: antioxidants, fat-based spread, fortification, infant nutrition, iron, micronutrient malnutrition, protein allergies

Introduction

The epidemiologic evidence for widespread multimicronutrient deficiencies is abundant [1–3]. The International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle, May 30–June 1, 2001, in Lima was motivated by an international concern for assuring micronutrient adequacy, especially in the youngest segments of populations in developing countries. This was also called for in the early 1990s at the Summit on Children (1990), the Meeting on Hidden

André Briend is affiliated with the Institut de Recherche pour le Développement and with the Institut des Sciences et Techniques de la Nutrition et de l'Alimentation, in Paris, France. He is a consultant for Nutriset, a company that produces fortified spreads. Noel W. Solomons is affiliated with the Center for Studies of Sensory Impairment, Aging, and Metabolism (CeSSIAM) in Guatemala City, Guatemala. Address for correspondence: André Briend, Groupe Nutrition Sante, ISTNA, 5 rue du Vertbois, 75003 Paris, France; email: brienda@cnam.fr.

Hunger (1991), and the World Conference on Nutrition (1992). More than a decade ago, these meetings issued calls for reducing or eradicating the prevalence of micronutrient deficiencies.

At the November 16–19, 1999, International Workshop on Micronutrient Supplementation throughout the Life Cycle in Rio de Janeiro, Brazil, the term "foodlet" was coined to denote a novel generic concept for a vehicle designed for flexible micronutrient intervention in infants and young children and served as a food in the context of meals [4]. There are diverse theories as to the semantic origins of the term. One theory is that "foodlet" is a combination of "food" and "tablet." However, an alternative theory is that the "let" is the generic French diminutive suffix, and that a "foodlet" meant a "little food." In fact, following the Brazil meeting, it was decided that the vehicle for supplementation in the trial led by the International Research Group on Infant Supplementation (IRIS) in Peru, Indonesia, Vietnam, and South Africa, would be a crumbly, flavored tablet: that is, a "foodLET," as discussed by Lock [5] elsewhere in these proceedings. Preliminary experience in conducting the IRIS I study, reviewed at the 2001 Lima workshop is presented by Smuts et al. [6]. As announced by Gross [7], a follow-up IRIS III study is planned, with the expectation of exploring the acceptability and micronutrient-nutrition efficacy of another delivery vehicle—the FOODlet. This would be the alternative expression of the "foodlet" concept; that is, a vehicle that is primarily a food (a "little food"), and culturally recognized as a food in its own right. The full presentation of a spread-based approach from the Lima workshop has been published in the pages of this journal as an independent contribution [8]; the present synopsis and reprise is meant to complement the other papers in these proceedings from the Lima workshop.

Fat-based spreads for tropical environments

Developments in applied technology related to the problem of rehabilitating malnourished children provided the springboard for the proposal of a novel, food-based approach to providing additional nutrients to children in their period of complementary feeding. The concept came from a fat-based spread originally known as a ready-to-use food (RTUF) [9], which was conceived as a replacement for the standard high-protein and energy-dense World Health Organization (WHO) recovery formulas (WHO 100 series) [10]. These standard formulas are liquid, milk-based beverages, which, once prepared for use in humid, unsanitary, tropical environments, have a short shelf life and rapidly become unsafe to consume.

A fat-based spread seemed to be an answer to the problem of providing nutrients to young children recovering from severe malnutrition [11]. Spreads are prepared by mixing vegetable fat with dry powdered ingredients, including dried milk products, pre-cooked soy flour, sugars, dextro-maltose, and a vitamin and mineral mix. Spreads have a fat content of at least 30% and an energy value of 478.4 kcal/100 g (2000 kJ/100g) or more. The fat component should have its viscosity and melting point adjusted to make the resulting product easy to store and swallow. More precisely, it should have a low viscosity at mouth temperature of 37°C [8, 12]. A fat with a relatively high melting point is best to prevent separation of components during storage at ambient temperatures, especially those encountered in the tropics, which can exceed 30°C. If the fat melts at too high a temperature, however, it will fail to melt at body temperature and an unpleasant mouth feel will result.

Advantages of such a spread include easy storage in tropical environments, where refrigeration is rare to nonexistent, and its potential to be introduced into the food system of a community as a specialty food for a specific age group. Bacterial and fungal growth require water and the appropriate nutrients. Spreads are, therefore, made without water and thus can be safely stored in the home without risk of pathogenic bacterial proliferation. The spread is a virtually anhydrous medium and hence resists microbiologic contamination. The main limiting factor for storage life is oxidation, which gives a rancid taste to the product, and leads to a decreased content of vitamins sensitive to oxidation. Through careful selection of primary ingredients and packaging under nitrogen into an aluminum foil container, it is possible to achieve a 12-month shelf life [12]. A much shorter shelf life is likely, however, when spreads are produced locally and not packed under nitrogen.

Fat-based spreads as micronutrient vehicles

The high acceptability of RUTF led to the notion of adapting the basic spread idea to create a multiple-micronutrient intervention product [13]. To begin, the development of a highly nutrient-dense spread as a supplement for children with low dietary intakes of vitamins and minerals was initiated in refugee areas in northern Africa. A controlled trial among Saharawi refugees, aged 30 to 64 months, showed this approach to be effective in treating anemia and partially reversing stunting in children [14].

As we look ahead to IRIS III, a series of diverse and specific questions arise with respect to adapting fat-based spreads as a FOODlet for multiple-micronutrient interventions in infants and toddlers.

Should the spreads be designed just as a vitamin-and-mineral-rich supplement?

The standard amount of nutrients to constitute a single daily dose of the recommended intakes (or multiple intakes) has been set as a precedent by the IRIS I experience [5] and was widely discussed at the Lima workshop. The formulation of a flexible spread, one which can accept a mixture and amount of micronutrients tailored to specific nutritional circumstances and population groups, seemed to be the highest agenda item in discussions related to the planning of the sequel protocol for IRIS III. The amount of spread needed to deliver a daily dose of micronutrients can vary from 10 grams to 100 grams per day. The advantage of using a higher-daily-dose spread is that it will deliver additional energy, but it is also more expensive than a smaller dose. However, if large volumes of spread are used to provide additional energy or additional nutrients, the volume needed may exceed what the target population can comfortably consume.

How do small children tolerate such spreads?

To be used in the IRIS III protocol [7], a spread must be designed specifically for supplementing infants and toddlers ages 6 to 24 months. This type of supplementation has not been previously attempted. Administering the spread by itself, as a snack, has the advantage of avoiding the risk of bacterial proliferation. Moreover, because spreads can be formulated to have a pleasant flavor, the unpleasant taste of soluble minerals can be disguised more easily than with aqueous products such as syrups. Also, a young child's ability to regulate water intake independently from food should be well established before a "snack spread" can be used. Because of their limited development of deglutition reflexes, infants ages 6 to 12 months may have difficulties swallowing a thick paste, even in amounts as small as 10 to 20 grams.

If young infants cannot eat the spread alone, it can be mixed into traditional porridges just before serving, which may be more tolerable. Spreads have a low viscosity at the temperature of any warm porridge, and can be added in the same way as butter or margarine. Porridges fortified by a spread should be consumed immediately after preparation; when mixed with a water-containing food, spreads do not keep their resistance to bacterial contamination. If the spread is to be mixed with other foods, consideration must be given to what potential inhibitors of trace mineral absorption are contained in those other foods. Potential inhibitors include calcium, dietary fiber, phytic acid, oxalates, and tannins.

Preventing oxidation of the spread product by its own ingredients

When it comes to the issue of oxidation, there is a dual concern. First, some of the nutrients, such as fat-soluble vitamins, are subject to oxidative destruction; second, the food constituents of the spread can be oxidized both by atmospheric gases and by its intrinsic ingredients. Fortunately, the surface area of the fat contained in the spread and in contact with oxygen from the atmosphere is low.

The double bonds in unsaturated fatty acids are susceptible to oxidative reaction, especially in the presence of transition metals such as copper and iron; as mentioned, oxidative reactions produce the off flavors of rancidity and the destruction of vitamins. However, the major micronutrient problem in the young child is that of iron deficiency. With respect to the iron fortificant in spreads, ferrous iron is 10 to 1,000 times more pro-oxidant than is ferric iron in vitro, depending on various factors, but especially the pH. Hence, soluble ferric salts may present a more desirable form for use in spreads. Encapsulated ferrous salts can represent an interesting alternative, provided the selected encapsulation method does not limit absorption.

Furthermore, the oxidative stability of the fatty acids and nutrients in the spreads could be improved by the addition of antioxidants. Because synthetic antioxidants, such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are not allowed under current regulations of foods for infants and children [15, 16], tocopherols and L-ascorbyl palmitate may be the only current alternatives. Citric acid may also decrease oxidation as a result of its metal-chelating properties. Even the proteins present in the spread can function as antioxidants through their ability to chelate metals and to neutralize free radicals.

Eliminating or limiting allergens in spreads

For infants, many protein-rich foods, such as milk, soy products, peanuts, and ground and tree nuts, are allergenic and their introduction into the complementary diet requires caution. The RTUF required the use of high-quality proteins; therefore, peanut butter was used when it was introduced in Malawi to replace part of the dried skim milk [9]. Peanut butter is inexpensive, available, familiar, and has a viscosity compatible with the spread. However, it has the disadvantage of containing potent antigens that can provoke severe allergic reactions [17]. Other possible ingredients include cow's milk (dried skim milk), which is expensive, and soy protein, which is less expensive but raises a greater concern regarding allergenicity. Because we are dealing with the period immediately after exclu-

sive breast-feeding for the IRIS III intervention, a more conservative and cautious approach might be prudent for this application.

The protein content of a spread can be changed when a food allergy is known to exist in the population or when introduction of novel proteins must be done with caution, such as in infancy. It is technologically possible to develop a protein-free spread that would still be valuable for improving the micronutrient quality of complementary food. This is precisely the context of the FOODlet spread. The resulting spread, however, might be more susceptible to oxidation unless compensated for by some of the antioxidant strategies discussed above.

Will a FOODlet spread be a sound economic choice?

The economic value of a spread as a FOODlet must also be assessed before recommending its use among the poor [18]. A clear principle has emerged—that the costs of fortificant minerals and synthetic vitamins are so low that they do not determine the cost of a fortified food. This expense is more related to the cost of the spread base itself and of the packaging required for its storage and protection [18, 19]. It can be estimated that the cost of spreads as FOODlet would be US $2 to $3/kg. If 20 grams of spread provides the daily micronutrient dose, this translates to US $0.04 to $0.06 per child per day. Moreover, because the cost of the spread base is higher than the micronutrients it contains, increasing the concentration of micronutrients in the spread will reduce the cost per dose. As noted previously, "A spread may be considered a good choice only if its inclusion among locally available foods results in a net reduction of the cost of a balanced diet—a realistic possibility, even in poor populations with limited purchasing power, with a well-designed spread." [8]

Conclusion

As noted by Nestel et al. [12]: "Spread development is not as advanced as sprinkle and tablet development, and further research is needed to improve the technology. Although none of the products is ready for widespread use, enough information is available to set research priorities and accelerate product development and implementation." Those of us involved in its development take it as a challenge to work through the numerous questions and queries that arise. As we evolve toward the IRIS III intervention, which contemplates the use of a spread-based FOODlet in young children, we expect to continue to resolve the issues raised by this truly diet-based multiple-micronutrient intervention.

Acknowledgement

We are indebted to the participants of the Boussingault Workshop, "New Food-Based Approaches to Achieve Micronutrient Adequacy in Complementary Feeding Diets: Technological Aspects," held in Paris, July 9–10, 2002, whose valuable insights have provided a framework for continued development of spreads as micronutrient vehicles in public health.

References

1. Calloway DH, Murphy SP, Beaton GH, Lein D. Estimated vitamin intakes of toddlers: predicted prevalence of inadequacy in village populations in Egypt, Kenya, and Mexico. Am J Clin Nutr 1993;58:376–84.
2. Maberly GF, Trowbridge FL, Yip R, Sullivan KM, West CE. Programs against micronutrient malnutrition: ending hidden hunger. Annu Rev Public Health 1994;15: 277–301.
3. Scrimshaw NS. The consequence of hidden hunger for individuals and societies. Food Nutr Bull 1993/1994;15: 3–24.
4. Gross R. Micronutrient supplementation throughout the life cycle. New York: UNICEF, 1999.
5. Lock G. The foodLET vehicle designed for and used in the IRIS I intervention. Food Nutr Bull 2003;24: S16–S19.
6. Smuts CM, Benadé AJS, Berger J, Hop LT, López de Romaña G, Untoro J, Karyadi E, Erhardt JG, Gross R. IRIS I: a foodlet-based multiple-micronutrient intervention in 6- to 12-month-old infants at high risk of micronutrient malnutrition in four contrasting populations: description of a multicenter trial. Food Nutr Bull 2003;24:S27–S33.
7. López de Romaña G, Gross R. IRIS III: proposal of a multicenter efficacy study using a high-energy, micronutrient-dense spread. Food Nutr Bull 2003;24: S39–S41.
8. Briend A. Possible use of spreads as a FOODlet for improving the diets of infants and young children. Food Nutr Bull 2002;23:239–43.
9. Briend A, Lacsala R, Prudhon C, Mounier B, Grellety Y, Golden MH. Ready-to-use therapeutic food for treatment of marasmus. Lancet 1999;353:1767–8.
10. WHO. Management of severe malnutrition: a manual for physicians and other senior health workers. Geneva: World Health Organization, 1999.
11. Diop el HI, Dossou NI, Ndour MM, Briend A, Wade S. Comparison of the efficacy of a solid ready-to-use food and a liquid, milk-based diet for the rehabilitation of severely malnourished children: a randomized trial. Am J Clin Nutr 2003;78:302–7.
12. Nestel P, Briend A, De Benoist B, Decker E, Ferguson E,

Fontaine O, Micardi A, Nalubola R. Complementary food supplements to achieve micronutrient adequacy for infants and young children. J Pediatr Gastroenterol Nutr 2003;36:316–28.
13. Briend A. Highly nutrient-dense spreads: a new approach to delivering multiple micronutrients to high-risk groups. Br J Nutr 2001;85(Suppl 2):S175–9.
14. Lopriore C, Branca F, eds. Strategies to fight anaemia and growth retardation in Saharawi refugee children. Rome: ECHO, CISP, INRAN, 2001.
15. Codex Alimentarius Commission. Codex standard for infant formula, Codex Stan 72-1981. Accessed at ftp://ftp.fao.org/codex/standard/en/CXP_021e.pdf on September 12, 2002.
16. Codex Alimentarius Commission. Codex standard for processed cereal-based foods for infants and children, Codex Stan 74-1981. Accessed at ftp://ftp.fao.org/codex/standard/en/CXS_074e.pdf on September 8, 2002.
17. Hourihane JO, Kilburn SA, Dean P, Warner JO. Clinical characteristics of peanut allergy. Clin Exp Allergy 1997;27:634–9.
18. Briend A, Ferguson E, Darmon N. Local food price analysis by linear programming: a new approach to assess the economic value of fortified food supplements. Food Nutr Bull 2001;22:184–9.
19. Bauernfeind JC, Lachance PA. Nutrient additions to food: nutritional, technological, and regulatory aspects. Trumbull, Conn., USA: Food & Nutrition Press, 1991.

IRIS III: Proposal of a multicenter efficacy study using a high-energy, micronutrient-dense spread

Guillermo López de Romaña and Rainer Gross

Editors' Note

The IRIS I study had a two-fold significance. First, it integrated four collaborating teams from various parts of the developing world, which resulted in more coordinated multicentric research. Second, the food-like tablet was only one possible format for delivering RDA-level micronutrients to infants and toddlers in the 10th to 16th month of life. IRIS II was an optional component of the original trial in which the placebo population would be crossed over to the multi-micronutrient arm for six additional months, bridging their 16th to 22nd months of life; this was conducted only in the Peruvian site. So, the workshop introduced a proposal to involve the same four teams and sites in a follow-up study (IRIS III), which would allow comparison of the efficacy and safety of identical nutrient doses in an alternative delivery vehicle, namely a fat-based spread. This paper provides insight into the planning and projection for such a study. More than two years have elapsed since the Lima meeting. The intention to execute the IRIS III protocol still exists, but the logistics and financing to carry out this next stage of research does not.

Abstract

There is an urgent need for the development of a high-energy, micronutrient-dense food, such as a spread, for clinical and emergency nutrition. The spread to be used in the International Research on Infant Supplementation (IRIS) III trial will contain carotene-rich palm oil as a source of vitamin A and energy, and heme iron from slaughterhouse blood as an iron source. All other micronutrients shall come from a pre-mix. The product shall be designed for young children, in particular, but can be consumed by adults, as well. An efficacy study will be conducted for six months in children 6 to 12 months old.

Guillermo López de Romaña is affiliated with the Instituto de Investigación Nutricional in Lima, Peru, and Rainer Gross is affiliated with UNICEF in New York City, USA. Address for correspondence: Rainer Gross, Chief, Nutrition Section, Programme Division, UNICEF, 3 UN Plaza, New York, NY 10017; email: rgross@unicef.org.

Key words: multi-micronutrient supplement, high-energy spread, IRIS, childhood malnutrition, infant malnutrition

Introduction

It is well documented that populations may suffer simultaneously from deficiencies of several micronutrients. At the same time, however, subgroups of these populations may also experience overall energy malnutrition, such as in cases of natural disaster, civil war, or chronic hunger. In these types of situations, young children and pregnant women are particularly vulnerable.

A high-energy, micronutrient-dense food, which can be used for different age groups, may help to bridge the gap of food intake until these high-risk groups are able to consume sufficient food. Several studies have tested the efficacy of such supplements in schoolchildren, adolescents, and adults. However, little is known about the efficacy of multi-micronutrient supplementation in infants. It is this age group that is most affected by these deficiencies. Due to their specific biologic characteristics, infants require specific micronutrient carriers. These must be safe, effective, acceptable, and affordable. A new type of energy-rich multi-micronutrient spread, which has been developed and tested [1], can be used for different target groups. Based on this experience, it has been suggested that such a spread be developed as a complementary food. Such a spread has the following advantages:

» Because the base of the spread is red palm oil, the spread provides additional energy, which is limited in the diets of many small children in developing countries [2].

» The red palm oil contains a high concentration of provitamin A carotenoids (β-carotene, α-carotene) and antioxidants such as tocopherols and tocothynols [3].
» Iron is provided in its organic form as heme iron. In this form, it will not compete with other trace metals such as zinc [4] or copper, it may avoid the risk of oxidative stress, and it allows a more stable form of a multi-micronutrient [5].
» Because the spread is anhydrous, it has been demonstrated to be microbiologically safe in tropical areas [6].

In the first study of International Research on Infant Supplementation (IRIS I), a common protocol was developed to be implemented simultaneously in several countries, which allowed results to be compared between the different sites [7].

Objective of the study

It is the objective of the IRIS III study to examine the efficacy of a multi-micronutrient spread given weekly as a complementary food to infants ages 6 to 12 months from micronutrient-deficient populations of different ethnic groups.

Population

We shall identify populations at probable need of micronutrient interventions based on existing evidence in the underfive segment as a whole of their impaired nutriture with respect to two index nutrients. Recruitment of infants will be undertaken in countries with 30% prevalences of anemia (Hb < 110 g/L) and 30% rates of low vitamin A status (serum retinol < 20 μg/dL) in underfives. To ensure statistical power, each group must enroll at least 65 infants. If any family has more than one child who is eligible to participate in the study, each child will be included and treated as a separate case. However, the children from one family will be assigned to the same intervention group.

The following exclusion criteria shall be enforced:
» Lack of signed informed consent
» Premature birth of the child
» Low birth weight: < 2500 g
» Congenital defects
» Chronic illness
» Severe wasting: < –3 Z-scores
» Fever: > 39° C
» Hemoglobin: < 80 g/L

All children who are excluded will be referred for appropriate assistance.

Study design

The efficacy study will be a 6-month-long, randomized, double-blind, placebo-controlled study. The study has two groups: (1) placebo, and (2) multi-micronutrient. In total, for each group, 14,000 spread sachets will be needed. This calculation projects 65 infants to be completing the study in each treatment group, from a total of 70 to be initially enrolled (estimated 6% attrition). Should the fortified spread be shown to have a positive impact on the infants in the multi-micronutrient intervention group, an equivalent number of fortified sachets will be needed to feed the placebo group for an additional 6 months, to comply with ethical considerations of equal benefits for all participants.

The spreads shall be administrated under rigorously supervised conditions on a weekly basis. To avoid any risk of microbiologic cross-contamination, the spread should not be mixed with complementary food such as porridge, but fed directly into the mouth of the infant. The spread shall be consumed 7 days a week (5 days with close supervision).

It is desirable that the spreads (placebo and multi-micronutrient) have the same color and are similar in form, taste, and texture. To assure standardization and quality control, the spread products and their ingredients shall be provided by one single producer, and shall be used in all study sites. Roche (Hoffmann La Roche, Basel, Switzerland via its subsidiary Roche Interamericana) shall provide the premix of the multi-micronutrients, except for provitamin A, vitamin E, and iron. The iron will be incorporated in the form of heme iron, which will be provided under the supervision of Fraunhofer-Gesellschaft, Munich-Weihenstephan, Germany. The energy source shall be α- and β-carotene–rich palm oil originating from the Malaysian Palm Oil Promotion Council. Nutriset in France shall produce the spread itself. Prior to launching the definitive intervention trials at the various sites, a pretest of the spread shall be conducted to test the stability and acceptability of the spread under field conditions.

The field workers shall visit the infants in their households weekly. During the visit, these staff members will directly observe the administration of the assigned dose of spread to assure compliance.

Multi-micronutrient spread

The multi-micronutrient–fortified spread to be used shall have the same levels of selected micronutrients as did the weekly supplement used in IRIS I (approximately twice the RDA), combined within a volume of spread weighing 20 grams. The nutrient composition of the spread is detailed in Table 1.

Conclusion

Similar to the procedures and rationales of the "foodlet-based" protocol of the IRIS I trials [7], the planning for IRIS III also builds upon the lessons learned in the multicenter execution of IRIS I [8]. The weekly format has been discarded. The innovative features of IRIS III include a shift to a new vehicle, the fat-based, anhydrous spread product [1], which presents much more like a food than a medicinal product, and is resistant to microbiologic contamination and has a long shelf-life in the tropics. To reduce the interaction of the iron source both with the fats of the matrix and with other nutrients, and perhaps to reduce the reactivity of the absorbed iron with the hosts themselves, heme iron will replace the inorganic ferrous sulfate employed in the IRIS I trial [7]. As long-term regular consumption of preformed vitamin A in the form of retinyl esters can lead to its excess consumption, the intervention approach for IRIS III is crafted for additional safety. By using the provitamin A carotenes in red palm oil, all risk of excess vitamin A accumulation can be avoided. An additional benefit of this product will be its rich contribution of vitamin E activity [3].

TABLE 1. One IRIS-III micronutrient dosage in the spread

Micronutrient Unit	Amount
β-carotene from palm oil (RE mg)	3
Vitamin D (μg)	10
Vitamin E (IU) from palm oil (tocopherol)	12
Vitamin B_1 (mg)	1.0
Vitamin B_2 (mg)	1.0
Vitamin B_6(mg)	1.0
Vitamin B_{12} (μg)	1.8
Vitamin C (mg)	70
Folic acid (μg)	300
Niacin (mg)	12
Iron (× 10 heme) (mg)	20
Zinc (mg)	20
Copper (mg)	1.2
Iodine (μg)	100
Selenium (μg)	40

The procedure for anthropometric measurements, blood sampling, and biochemical analysis shall be followed according to the protocol of IRIS I [7].

References

1. Briend A, Lacsala R, Prudhon C, Mounier B, Grellety Y, Golden MH. Ready-to-use therapeutic food for treatment of marasmus (letter). Lancet 1999;353:1767–8.
2. Scrimshaw NS. Nutritional potential of red palm oil for combating vitamin A deficiency. Food Nutr Bull 2000;21:195–201.
3. Nagendran B, Unnithan UR, Choo YM, Sundram K. Characteristics of red palm oil, a carotene- and vitamin E–rich refined oil for food uses. Food Nutr Bull 2000;21: 189–94.
4. Solomons NW, Jacob RA. Studies on the bioavailability of zinc in humans: effects of heme and nonheme iron on the absorption of zinc. Am J Clin Nutr 1981;34:475–82.
5. Mäurer A, Schümann K. Abattoir blood used in foods: an example of nutrition-environment interaction. SCN News 2000;21:32–3.
6. Lopiore C, Branca F. Strategies to fight anemia and growth retardation in Saharawi refugee children. Rome, ECHO, CISP, INRAN, 2001.
7. Gross R. Micronutrient supplementation throughout the life cycle. New York: UNICEF, 2001.
8. Smuts CM, Benadé AJ, Berger J, Hop LT, López de Romaña G, Untoro J, Karyadi E, Erhardt J, Gross R. IRIS I: A foodlet-based multiple-micronutrient intervention in 6- to 12-month-old infants at high risk of micronutrient malnutrition in four contrasting populations: description of a multicenter trial. Food Nutr Bull 2003;24:S27–S33.

Multiple micronutrient deficiencies: Future research needs

Rainer Gross and Noel W. Solomons

Editors' Note

The IRIS I (completed) and IRIS III (projected) multi-center protocol studies are intended to be "efficacy trials" to evaluate the nutritional impact (biochemical and functional indicators) of various formats for delivering RDA-levels of single or multiple micronutrients in a "foodlet." Within the discussion that surrounded the presentations at the Lima workshop, issues of "safety evaluation" and assessment of "effectiveness" and "efficiency" arose. This brought in elements of a larger research agenda that had been considered for the straightforward execution of the IRIS I field trial. In the breakout working-group session on research needs, more generic considerations were raised related to the emerging impetus to design and conduct multi-micronutrient intervention investigation. This final paper was not actually part of the invited plenary talks on the program in Lima, but emerged as an attempt to develop and formalize the generic considerations for research—including design, procedures, and ethics—as our group and others go forward around the world.

Abstract

There has been a rising current of calls for a moratorium on international nutritional research in favor of an investment in intervention programs, per se. The topic of multiple-micronutrient supplementation reviewed at the International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle (May 30–June 1, 2001) has confirmed once again, however, the intimate interaction between program development and a supporting agenda of applied research. The areas of research required to produce successful intervention programs include bio-logic availability, safety and efficacy, communications and behavior, effectiveness, cost-effectiveness (efficiency), and food and pharmaceutical technology. Attention to safety and surveillance for unintended adverse effects has acquired new relevance as we analyze the multi-center International Research on Infant Supplementation (IRIS) I studies. All professionals involved in research projects in this area must assure both the quality and reliability of investigations and adhere to the highest principles of ethical conduct of research in human studies. The fundamental principles of research design and hypothesis development, quality assurance, reliability of measurements, and sound and unbiased interpretation of findings apply to all experimental science, and must be guaranteed for this mission. Agencies, academic institutions, and industry alike must work to create a system in which researchers can uphold these standards, and realize at the same time that the area of multi-micronutrient supplementation in developing countries can be a fertile area for training future researchers.

Key words: multi-micronutrient supplementation, micronutrient deficiency, research design, safety, efficacy, ethics

Introduction: The mission of research persists

Over the years, many things have been announced and declared prematurely. It is said that after reading a notice of his own demise in the obituary pages of a major newspaper, the satirist Samuel Clemens (Mark Twain) replied with a letter to the editor as follows: "Rumors of my death have been greatly exaggerated. Mark Twain." Similarly, in the 1960s, a group of theologians who were galvanized around the book *The Secular City: Secularization and Urbanization in Theological Perspective* [1] by Professor Harvey Cox of the Harvard School of Divinity, developed the "Death-of-God Theory," which stated that, even if there had once been

Rainer Gross is affiliated with UNICEF in New York City, USA. Noel W. Solomons is affiliated with the Center for Studies of Sensory Impairment, Aging and Metabolism (CeSSIAM) in Guatemala City, Guatemala. Address for correspondence: Rainer Gross, Chief, Nutrition Section, Programme Division, UNICEF, 3 UN Plaza, New York, NY 10017, email: rgross@unicef.org.

a Divine Creator, the rationalism of humankind had evolved to the stage in which it was no longer necessary to believe in a supreme being. The emergence since the 1980s of fundamental fervor among all of the world's religions belies this theory.

In the field of international nutrition research, we have passed through a similar discussion of the demise of a role and utility for investigation. The gauntlet was thrown down in 1993 with the publication of the Martin Forman Memorial Lecture "Sliding toward nutrition malpractice: time to reconsider and redeploy" by Alan Berg [2, 3]. It called for a virtual moratorium on investment in international nutrition research, with diversion of resources into programs instead. A colleague [4] went even further, asserting that the entire discovery needed to solve the nutrition problems was in hand, and that the only legitimate investment for nutrition was in implementation of actions.

The suggestion that investment in international nutrition research is no longer necessary seems to rank with the premature obituary of Mark Twain and the "Death-of-God" theology. Indeed, the litany of important new insights into nutrition biology and new applied nutrition for assessment and intervention just since the debate sparked by the 1993 Forman lecture would fill the pages of an issue of this journal. It is reasonable, therefore, that we strengthen our capacity to select the still-relevant research topics for the area of multi-micronutrient deficiency, and to perform that research with skill and quality.

Hidden hunger comes out of hiding

The years following World War II were filled with the optimism that solving the world's malnutrition problems would be a matter of closing the "protein gap" between the production of dietary protein sources and population explosion in low-income nations [5]. In fact, the production of food crops and livestock has kept pace with population expansion [6], and most diets deliver adequate protein when energy needs are met. Another aspect of the undernutrition paradigm, however, has begun to occupy public health concern—malnutrition of vitamins and minerals.

It was the research of Sommer et al. [7, 8] in the Aceh Province of Indonesia that extended the importance of vitamin A from nutrition blindness to increased mortality from childhood infections and sparked a surge in interest in micronutrient deficiencies. Developmental deficits resulting from deficiencies of iron [9] and iodine [10] were identified, and the concept of "hidden hunger,"—insidious deficiencies from nutrients present only in minute amounts in the diet—emerged [11–13].

The response to hidden hunger was grounded in vertical policies and programs involving each of the aforementioned nutrients, but in formats of single-nutrient interventions. For vitamin A, this meant distribution of retinyl palmitate A capsules [14] or fortification of common vehicles with vitamin A [15, 16]. In the case of iodine, salt iodination was the prime focus [17], but other solo modes of delivery of this nutrient were explored [18, 19]. Iron delivery at the public health level has traditionally been part of a dual-nutrient intervention, combined with folic acid, in prenatal supplements provided to pregnant women.

Multiple-micronutrient supplementation: new research opportunities and requirements

Where the diet is nutrient-rich and the environment benign, one can assume that all of the nutrients needed for growth and nutriture will be consumed, absorbed, and retained. Cultural evolution, however, has forced human populations to subsist on an increasingly narrower variety of food items, dominated usually by one or two staple crops: grains, tubers, or both [20, 21]. The evolutionary transition of humans from hunter-gatherers to agriculturalists reduced the micronutrient density of the diet. As a consequence, multiple micronutrients are consumed below recommended amounts by all but the most affluent of societies [22]. Combined with parasites, infections, and chronic inflammatory stress, all of which reduce retention of dietary nutrients [23], humans became vulnerable to having a lower reserve of micronutrients than is necessary for optimal physiologic and biologic function.

There is a growing roster of micronutrients that may be inadequate in segments of human populations and concurrently deficient in many individuals in deprived populations, namely, iron, vitamin A, iodine, fluorine, zinc, folate, vitamin B_{12}, and selenium. Iron, vitamin A, and iodine are the triad of micronutrients that galvanized interest during the hidden hunger era. Fluorine, dissolved in water supplies as fluoride, is a protective factor against dental decay, and adjustment of water concentrations or additions of fluoride to salt have been initiated.

Among the newer areas of interest are zinc, folate, vitamin B_{12}, and selenium. Some have speculated that low zinc intakes and absorption contribute to linear growth retardation in populations around the world [24]. Recommended dietary allowances (RDA) for folate have doubled since the recognition of its protective role against neural tube defects (NTD) [25]. Rates of NTDs have been found to be high in many low-income nations. Religious proscription, poverty, or both can limit the intake of foods of animal origin, which in turn reduces intake of vitamin B_{12}. Widespread *Helicobacter pylori* infection, moreover, may be contributing to gastric atrophy in residents of

developing countries, compromising their ability to absorb vitamin B_{12}. Soils in many parts of the world are depleted in selenium. This was a factor in the susceptibility of many Asian populations to Keshan's disease [26]. However, the example of selenium shows us that the problem is even more complex, because we know that selenium deficiency can be partly responsible for the expression of iodine-deficiency manifestations [27, 28].

Hence, a school of thought in public health nutrition issued a dissent to the dominant approach to deal with micronutrient deficiencies on a nutrient-by-nutrient basis. This was spurred on by the emergence of the concept of intermittent-day supplementation as an intermediate point between campaigns of massive, high-dose supplements and programs requiring daily administration of lower doses [29]. Such experiences began to generate the bases of routines for research design dealing simultaneously with multiple micronutrients. Subsequently, the philosophic and physiologic underpinnings of the rationale for combining multiple micronutrients in both research [30] and intervention programs [31] have been initiated.

Several workshops have been convened over recent years, in Singapore (1998), New York City (1999), Rio de Janeiro (1999), Cape Town (2000), and most recently in Lima, Peru (2001) by a group of professionals from academia, industry and policy agencies. Within the Sub-committee on Nutrition of the Administrative Committee on Coordination of the United Nations' agencies (currently the UN Sub-committee on Nutrition), a commission on micronutrients has been operating for some years, and it has been actively examining the evidence supporting the combination of micronutrients in interventions and their administration on intermittent schedules, such as weekly or biweekly.

Technical and ethical considerations

The research needs for studying micronutrient deficiencies can be interpreted at two levels: (1) the ways to conduct it correctly (tactics), and (2) the selection and priorities of research issues (strategy). The former relates to the quality and rigor of the execution of the research to assure that hypotheses and objectives are correctly addressed. Researchers must be thoroughly familiar with the types of research that apply to the field and the options, opportunities, caveats, and limitations that are inherent. Because special biologic and epidemiologic issues are related to countries with scarce resources for training and equipping facilities, it is essential to recognize potential weaknesses prior to moving to the second level, which is that of the specific priority areas for investigation.

Assessment of the situation

Where are interventions warranted? Where are they contraindicated? To address these questions, a series of diagnostic indicators for at-risk populations are needed. Three strategies can be employed to assess the nutrition situation: (1) social and environmental predictors alone, (2) biomarkers of exposure and status alone, or (3) a combination of both classes of indicators. Although much of the concern for research is related to its development and implementation, it cannot be overlooked that knowing where and when to—and not to—intervene is an important concern. Diagnostic tools that are both acceptable and innocuous but also reliable and cost-effective are needed for many of the nutrients of public health interest. Moreover, indices of nutrient overload are needed to avoid causing harm to some individuals in a population in which other, more deficient segments are being benefited by a micronutrient intervention.

Safety issues

It is no accident that the classic expression for the suitability for use of a medicine is "safe and effective" (in that order). With respect to multinutrient deficiency research, safety should also occupy a position of supremacy. At the scale of the study population to be enrolled in a study, precautions should be made to assure safety. But within the design of research, even if it begins by looking at efficacy as the primary outcome, there must be allowances to detect any negative effects of the intervention.

An implicit aspect of this concern for safety is that adding more micronutrients to an individual's diet, even in those at risk of micronutrient deficiency, may have negative consequences. The following three possibilities must be considered [32]: (1) that health protection can be achieved by inducing or maintaining a lesser nutrient status in a population, (2) that damage to health can result from dosing individuals with additional micronutrients in interventions, and (3) that nutrient imbalance can be produced by high-dose supplementation by a single micronutrient.

Being faithful to the mission of "safety first" is often a technical matter, assuring that potential adverse effects are measured, recorded, and analyzed. Growth and morbidity are two such gauges that can pick up untoward effects of micronutrient supplementation. If animal literature or anecdotes provide other insights into possible risks of increasing intakes of a nutrient or a combination of nutrients, the indicators related to these effects must be designed into the research.

Ethics of safety studies

On one hand, the ethics of including placebo (no-treat-

ment) treatment groups have been questioned in the context of efficacy studies, as one group does not stand to gain any additional benefit if a no-treatment arm is included in the design. Conversely, in a technical sense, one cannot interpret the safety of a dosing scheme with single or multiple micronutrients without including a no-treatment group.

The policy community has a special responsibility to the public to assure that the interventions recommended and implemented will be safe, as well as effective. Risks from micronutrient exposure may be different for the general population compared with certain subgroups, such as those with HIV infection [33], in whom extra amounts of one or another vitamin or mineral may produce a shorter survival. These hypotheses must be dealt with in research, and their findings addressed in policy. But even the general population is not immune to adverse effects of essential micronutrients, such as when iron is administered to those who are already iron adequate [34, 35] or when β-carotene supplementation produces adverse effects in cigarette smokers [36]. Academic and industrial communities can support this mission by assuring that research is conducted with the highest standards for protection of research subjects and that efforts are made to eliminate the risk that the intervention will have adverse effects on members of the target populations.

Efficacy

Efficacy is a measure of the biologic impact of an intervention under controlled conditions. In the present context, an efficacy study would address the question of whether a specific cumulative dosage of micronutrients or a micronutrient-sparing procedure would result in a specific quantifiable effect, independent of confounding behavioral factors. Prior to any implementation of a program, one wants to know whether or not a measure "works" in a human biology sense. As such, efficacy studies are performed under carefully controlled, supervised, and regulated circumstances, assuring a quantitative delivery of micronutrients and minimizing sources of confounding. Bioavailability studies would proceed as a prelude to cohort studies in the field, and can be considered with this topic.

Research design

Before any other considerations, the construct validity of a study must be intact. By construct validity, we mean the theoretical (biologic) linkage between cause and effect. For instance, if we are going to use improvement in night blindness as the indicator of an efficacy study, we must be certain that a deficiency of the nutrient of interest can be responsible for the condition. For questions of vitamins A or E or zinc, dark adaptation performance would be a reasonable variable; for vitamin D, calcium, or vitamin B_{12}, there is no known dependency of this ocular function on the nutrient.

The process of selecting variables must consider other issues. There are two classes of variables that can be used to assess impact in prospective, cohort trials of micronutrients: (1) static indices, and (2) functional indicators [37, 38]. On the static side, increased exposure to a nutrient can influence the total-body reserves or the body pool of a given nutrient. Measures that reflect the presence of a nutrient in a chemical or biochemical manner, based on the concentrations of an analyte (nutrient, metabolite) in a body fluid or tissue, are classified as "static" indices. Levels of nutrients or metabolites of interest in blood (plasma, serum, red cells, white cells, and platelets), and in urine, saliva, tears and cerumen constitute the static indices of body fluids. Biopsy materials for tissue analysis can range from non-invasively collected fingernails, toenails, hair, and buccal mucosal cells, to less innocuous biopsies of gingival and intestinal tissues, skeletal muscle, bone, and bone marrow.

On the functional side are the biochemical and physiologic reactions or whole-organism behaviors and performances. These include measures of functions that can only be a maximal individual capacity if one or a number of nutrients are in adequate supply. Dark adaptation is a classic example of a functional measure that depends on the intactness of nutriture for vitamin A, zinc, and vitamin E. Growth of children is another function dependent upon many macro- and micronutrients. A long list of nutrient-dependent functions have been exploited for nutrition assessment [38]. Another dimension of functional assessment is to evaluate the state of homeostatic regulation of a nutrient's metabolism. If the body manifests excessive uptake or retention of a regulated nutrient, it suggests total-body deficiency; conversely, if there is reduced uptake or excessive excretion, this signifies adequacy or overload.

One of the limitations of functional assessment is person-to-person variation in the constitutional functions. Often it is necessary to administer a nutrient to determine whether the functional performance was nutrient-limited. Moreover, other conditions besides malnutrition can limit functional capacity. A functional test requiring visual acuity may be confounded in the elderly by underlying ocular diseases of aging.

Having the appropriate sample size and plan for analysis is essential in all types of multiple-micronutrient investigations. If the measurement of interest is variable, either multiple measurements in the same subject or a large number of subjects may be required to avoid a type II error in testing the null hypothesis of a treatment effect. The necessary sample size must be accomplished for the research results to permit valid conclusions. How the data will be expressed and how

tests of hypotheses will be made are additional critical features of research design that can relegate a study to the status of useless or misleading. Interpretation of the study should also be favored by the design. When the issue is multiple micronutrients, one must provide opportunity, whenever possible, to assess interactions (synergistic, antagonistic) among micronutrients that are provided together in a trial.

Quality control

It is not enough simply to plan and execute collections and perform measurements. Quality control is a fundamental concern. A series of pitfalls are latent in the process of collecting data. How reliable is the test of effect? It can be unreliable because it provides the wrong answer, i.e., it is inaccurate or invalid. It can be unreliable because it provides variable answers from test to test, i.e., it is unstable or imprecise. Detecting inaccuracy and imprecision, and correcting them as best one can, are obligations of good research practice.

In some nutrient trials, namely in those in which an abnormal nutrition status is to be corrected by the intervention, the sensitivity (ability of a test to detect true abnormals) and specificity (ability of a test to detect true normals) of the measures are important. The entire gamut of quality-control issues comes into play with a new innovation in static indicators for field studies—when capillary blood samples are either preserved as liquid supernatant or applied to filter-paper cards and then dried to produce dried blood spots [39, 40] or dried serum spots [41]. This format is friendly to field investigation for the small amounts of blood involved, safety from viral transmission, and the lack of need for a cold-chain for storage and shipping.

Bioavailability indicators, absolute and relative

Among the questions to be asked at the efficacy stage in multi-micronutrient studies is whether—and to what extent—nutrient(s) are absorbed from a given preparation of supplement. The concept of "bioavailability" first emerged in the field of pharmacology, and was later adapted to the issues of uptake of nutrients and food constituents in the field of nutrition.

When a nutrient (or drug) is taken by mouth, it has three possible fates: (1) it can be taken up systemically into the body, (2) it can remain in the intestinal lumen or wall, only to be excreted intact in the feces, or (3) it can remain in the intestinal lumen or wall, outside of the inner systemic compartment, but be metabolized or destroyed in situ.

Strategies to determine uptake of a nutrient can follow one of two approaches in a bioavailability experiment [42]. One is to evaluate the amount or percentage of the administered dose that crosses the intestine and enters the systemic compartment; the other is to measure that which gets left behind, usually by collecting stool samples quantitatively and measuring the fecal nutrient content. A severe confounding factor for the latter approach, however, is any colonic degradation of the analyte(s) of interest.

The absorptive response can be evaluated in either *absolute* or *relative* terms. The absolute absorptive response takes into consideration the net quantitative amounts (grams, milligrams, moles) of nutrients taken up by the body. Relative absorption refers to the comparison between the appearance of nutrients in the bloodstream, tissues, or urine after a standard reference dose and that produced by the nutrient given in another form, such as in its native food matrix or incorporated into a meal. The latter approach has advantages insofar as it requires less prolonged and rigorous collections to determine effects and differential effects. However, it lacks the quantitative validity of determining what percentage of an administered dose actually becomes available to the host.

Ethics of efficacy studies

The primary ethical issue for efficacy studies has been discussed above; it is that of safety. Suitable designs combine considerations of both healthful impact and potential adverse effects within the same context. The principle justification for a placebo (no-treatment) arm of a study is really related to safety concerns. It also improves the interpretation for definitive conclusions on the efficacy side. If, for any reason, a treatment arm without any potential to benefit the subjects is proscribed, a dose-response arrangement with a range of concentrations of the micronutrients can be assigned, or various combinations of micronutrients eliminating one nutrient from each treatment can allow for interpretation of efficacy (and safety) even without a no-treatment, placebo arm to the study.

With regard to collecting tissue or body fluid samples, minimum offensiveness or discomfort to the community or its participants is warranted. Urine and breast milk and even buccal mucosal swabs produce samples that are less objectionable than those of human blood. In an era of HIV transmission risk, these biologic samples are also safer for handlers and laboratory personnel [43]. Recent advances in microanalysis increasingly allow minute amounts of capillary blood from finger pricks to provide for assays that previously required milliliters of venous blood [43].

Finally, a plan to handle situations of nutrient deficiency uncovered by the examination must exist, and be coherent and ethical. The efficacy study implies that undernourished individuals will be enrolled and observed for a period of time to see if a different rate of improvement is observed between placebo and treatment cohorts. The degree of severity of deficiency that would be unattended on discovery and left to be fol-

lowed over time must be defined and justified, and the length of time that any degree of abnormal nutrition would go without redress must be reasonable from an ethical point of view. A criterion of severe nutrition status that would require immediate response should be established, such that all children initially at that point (or reaching that status during the observation interval) would be offered therapeutic assistance from the study's resources. Moreover, after concluding a study, investigators should be prepared to assure that all persons remaining in an abnormal nutrition state will be provided access to appropriate therapies to return them to a state of adequate nutriture.

Effectiveness

Effectiveness is the measure of impact of a public health intervention when it is introduced into the regular health system, rather than with the excessive control of a research efficacy format. Does the desired biologic effect persist under all of the conditions of "real life"? It is unlikely that there will be a simultaneous comparison group. The "historical" control of the stable prevalence of deficiency prior to the intervention can be used as a reference, but it is a weaker standard than the placebo- or dose-controlled formats of efficacy trials.

Because the context of effectiveness is in the "unguided" and "unsupervised" application of the intervention, one can document both process indicators as well as product (impact) indicators. Process indicators are the chain of actions and behaviors that are preconditions to the intervention's having the possibility of producing an effect. Such indicators would include the availability of the intervention's product, the distribution of products to stores, the number of purchases of the product, and the servings delivered within the home, etc. Also, if educational or promotional components exist, a process variable would be attendance of mothers at the communication points or events. These represent the explanatory variables that would allow interpretation of overall effectiveness measurement. If the process is not intact, the impact is unlikely to exist. However, even with the most favorable processes, the expected biologic impact may not occur. Hence, the fundamental indicators of effectiveness are those of the effect produced by the intervention. The same impact indicators as for efficacy are implied, as it is the biologic effect that represents the promise of improved nutrition status.

Ethics of effectiveness studies

The issues of placebo control are not part of effectiveness studies, because this type of inquiry covers only populations in which measures have been implemented on a routine basis, whether at a pilot scale or definitively. The ethical issues related to safety, convenience, and risk for making nutrition-impact measurements on the sentinel subjects in effectiveness studies are identical to those of efficacy studies. To the extent that receiving information on a subject's nutrition or physiologic status is considered to be a benefit of study, however, effectiveness studies might differ from those of efficacy. No formal control group is included, but a "similar" population, outside the coverage zone for the intervention, might be enrolled for comparison; the only benefit for such participants might be to gain information on personal nutrition status. For either the comparison group or the group covered by the program, the evaluation of nutrition status might reveal a deficiency state. Ethical considerations of whether just to inform the caretakers (and indicate that therapeutic care is required), or to be more proactive (and offer assessment and curative services from the investigation team itself) must be explored before the evaluative phase of an effectiveness study is taken to the field.

Efficiency

The final concept is efficiency, which relates to the cost implementing and maintaining an efficacious and effective intervention program. It can be measured in terms of the brute resources necessary and the effects obtained. Such expressions may be the investment of "x" amount of funds to increase the mean height of the mean stature of the population by 2 cm, or to reduce the number of stunted individuals by half. The level of outlay can also be identified. For instance, the amount that a whole society would have to mobilize for an intervention in the collective public domain could be estimated, or that which a consuming family would have to spend to obtain the nutrition-promoting effects of a commercial product could be modeled into efficiency research.

Ethics of efficiency studies

The ethical issues of this type of evaluation derive from those discussed for efficacy and efficiency, including using minimally invasive measurements and formulating a plan to respond to discovered cases of abnormal nutrition status. The full analysis of efficiency depends upon knowing effectiveness with the aforementioned ethical issues. If direct household interviews are required, however, one can enter into the sensitive area of individual incomes. Informants are often very reluctant to provide full disclosure in this area. Researchers must assure confidentiality of information to protect the interests of the subjects. A moral-ethical implication comes from the final efficiency evaluation. If it turns out that benefits come at a very high cost to the population benefited, one faces a serious value judgment as to whether the measure should be recommended for continued implementation.

Research in communications and behavioral sciences

Aside from the biomedical and biologic variables implicit in the research areas discussed so far, issues of behavioral science and applied communication are also relevant. For instance, to understand processes of compliance (or non-compliance) at the stage of effectiveness evaluation, one can develop and administer research questionnaires or use informants in open-ended interviews or focus groups. Because this research is applied to specific modes of intervention, it cannot be conducted in the abstract, but rather with a specific micronutrient measure in mind. The objectives of the research are to document the current patterns of behavior in a population and to explore ways of changing behavior that are conducive to the participation in one or another micronutrient intervention with demonstrated biologic efficacy. So important are linguistics and culture that involvement of community members in social science research is virtually essential.

With respect to communication, research on fine-tuning and crafting messages to the public at the launch and during the maintenance of public health multimicronutrient interventions is an important part of the investigative agenda. Two primary issues to be investigated are how to gain access to the population and how to transmit a clear message. In theory, the instruction for a certain positive conduct could come through formal (schools, classes), informal (newspapers, television, internet), or non-formal (family, friends) modes of communication. Before deciding upon one or another medium, researchers should conduct formative research on how effectively the various modes can reach the population of interest. The more complex the behavior required, the more formality is needed to communicate the message clearly. The art of making any message clear and comprehensible, however, is the product of formative research in which social psychology, linguistics, and motivational aspects of the target population are understood. For the same reason that we use the term "hidden hunger" to denote micronutrient deficiencies, the "intangible" nature of micronutrients often makes it difficult to convey their importance to unaccustomed populations. Emphasis on the vehicles that need to be consumed and the benefits to be achieved may be more successful in achieving the desired behavior.

Ethical considerations in communications and behavior

Measurement of social science variables is inherently less invasive and less hazardous, because these variables do not involve human biologic materials; nonetheless, ethical issues arise. The basic issues of anonymity and confidentiality are fundamental. Autonomy is also important, and the participants must be *voluntarily* study participants. Often, however, one cannot be completely forthcoming as to the purposes of research, and measured deception (disguising true motives or surreptitiously observing) is often permissible at the behest of a sensitive human research committee.

To the extent that there are fewer risks and inconveniences in the measurements of these behaviors, there are also fewer benefits derived from their study. With nutrition status measures, one can often help the participants directly with remedial nutrition. The benefits, if any, that derive from behavioral research will apply only indirectly—if at all—to the subjects of study, and only in the long run with the implementation of programs.

With respect to communication, ethical considerations here have to do with the honesty and transparency of the use of final data. To the extent that communication techniques can alter behavior, it is important that they be mobilized in the genuine best interest of the health and nutrition of populations. More than the formality of ethical rules, it is the true morality and values of the investigators behind communication research and implementation that are important to protect the public from any damage in efforts to conquer micronutrient malnutrition.

Strategic priorities in research: mission

The previous section has covered the fundamental principles, caveats, and ethical considerations regarding the gamut of research studies that are part of the agenda for multi-micronutrient supplementation. The agenda, itself, however, does not arise from this listing of generic research principles without the application of a set of research priorities. If, indeed, the previous section addressed the tactics of the micronutrient research mission, this section deals with the strategy for that mission. From where do the priorities for specific research projects arise? The agenda for research on multi-micronutrient deficiencies must have two characteristics. First, it must derive from a convergence and consensus within the field of interested professionals; second, it must be appropriate and desirable to attract necessary resources.

Some insight into research priorities for the field can be gained from examining the outcomes of two meetings on this topic held over a 2-year period. The first was the workshop, Micronutrient Supplementation Throughout the Life Cycle, in Rio de Janeiro (November 1999) [44]. The range of specific research topics from annex 3 of that workshop's report [44] is reproduced in table 1. The other was the International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle, in Lima, Peru (May 30–June 1, 2001), and notably the product of its working group #4, whose agenda and matrix for discussion of research topics in Lima is presented in table 2.

Although different category headings are used to

TABLE 1. Multi-micronutrient research topics from the report of the Workshop on Micronutrient Supplementation throughout the Life Cycle, November 16–19, 1999 in Rio de Janeiro, Brazil*

Category 1
Biochemical, physiologic, and epidemiologic determinants of multi-micronutrient deficiencies
1.1 Age groups and physiologic status (e.g., pregnancy, infection, contamination)
1.2 Socioeconomic status
1.3 Ethnicity

Category 2
Functional indicators
2.1 Micronutrient status in different ages and physiologic states and functional outcomes

Category 3
Efficacy of multi-micronutrient supplementation in different age groups and physiologic states
3.1 Efficacy of daily/weekly dosing of single micronutrients (B vitamins, folic acid, niacin)
3.2 Efficacy of daily/weekly dosing of combined micronutrients

Category 4
Effectiveness of multi-micronutrient supplements
4.1 Effectiveness of micronutrient supplementation in single population groups
4.2 Effectiveness of micronutrient supplementation in the whole population (life cycle approach)

Category 5
5.1 Communication

Category 6
Cost considerations
6.1 Costs of multi-micronutrient supplementation
6.2 Cost-benefit

Category 7
Diagnostic indicators
7.1 Simple food intake/frequency indicators for multi-micronutrient deficiency
7.2 Simple biochemical markers for multi-micronutrient deficiency

Category 8
8.1 Product development of non-drug supplements

* Adapted from [44].

TABLE 2. Brainstorming agenda/matrix from working group #4 on research needs at the International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle, May 30–June 1, 2001, in Lima, Peru*

Efficacy/safety	Dosing Low birth weight Pregnancy Functional vs biochemical outcomes Disease issues
Bioavailability	Nutrient interaction Food/carrier
Delivery issues	Vehicles Fat Powder vs tablet vs liquid Bioavailability Acceptability
Behavioral issues	Compliance Cultural perception Dosing schedule Communication
Cost-benefit	Relation to efficiency Affordability issues
Assessment	Magnitude and severity of different micronutrient deficiencies Cut-off in different age groups Need for new assessment methods Intervention: biochemical outcomes Intervention: functional outcomes/disease issues not attributable to single micronutrient: growth, morbidity, stress indicators: efficacy/safety

* Adapted from [45].

denote the topics of each workshop, there is much similarity between the topics of the two workshops. In the Rio meeting (table 1), category 2 (functional indicators) and category 7 (diagnostic indicators), as well as the issues in category 1 (epidemiologic determinants of multi-micronutrient deficiencies) are all reflected under the five bullet-points of "assessment" in Lima (table 2). Category 6 (cost considerations) from Rio and "cost-benefit" from Lima are also essentially identical.

The issues of Rio's category 3 (efficacy of multi-micronutrient supplementation in different age groups and physiologic states) are covered by the five headings of "efficacy/safety" from Lima. In Lima, the group went much farther, however, and this is where the departures from the Brazil process begin to emerge in the later Peruvian considerations. Notable is the absence of safety as a specific component—or even any explicit written mention of the word—in the Rio de Janeiro meeting, at which the IRIS study was launched. Two years later, when preliminary data from IRIS were presented in Lima, it was not hard to understand why safety was both mentioned and ranked as the primary issue for the field. Preliminary indications of a potential adverse effect of iron supplementation emerged from at least two of the field sites.

The social sciences issues in multi-micronutrients are one of the major disconnections between the two workshops. In Rio, category 5 was "communication," with no further detail or adorning information (table 1). One must, then, read the text of the report [44] for a sense of the context given to communication research at that workshop. The meeting in Rio de Janeiro identified a series of audiences for the communication messages to be targeted to. The primary audience comprised those who were deficient themselves

(consumers), or their caretakers if they were minors. The secondary audience were those who would influence the primary audience, including community opinion leaders, health professionals, family members, and peers. Finally, the tertiary audience included policy and decision makers, donors, academics, professional societies, and the media. Inputs of the latter are needed to make any program a success.

In the Lima workshop (table 2), communication fell as a bullet-point under "behavioral issues," along with cultural perception, compliance, and dosing schedule. Perhaps what is common to the social-science component is a need for a two-stage research consideration. The first tier would be a situation analysis to identify the knowledge, attitudes, practices, and perceptions surrounding the behavioral issues. The second would be the applied research—based around the former—that shapes the most effective messages to communicate and advocate for the program to each of the three levels of audience.

Also interesting is the positioning in the Rio table (table 1) of communication, i.e., between the categories of *efficacy* and *effectiveness* (above it) and that of cost-benefit or what can now be called *efficiency* (below it). This calls upon us to accept the notion that successful communication is, indeed, the link that makes an effective program appropriate for its cost. Logically, however, this is not a reasonable hypothesis. A more logical rationale is that communication be the link between the biologic efficacy of a multi-micronutrient intervention and its continued effectiveness of impact at the public health level.

The final category from the Rio meeting makes an explicit statement about the formulation of the intervention, i.e., as a non-drug supplement. The Rio meeting gave birth to the concept of the "foodlet" (i.e., food plus tablet), which was the basis of the IRIS protocol. Some workshop participants were disappointed with the actual foodlet. Most saw it more as a medicinal tablet than as a food item. If the philosophic and practical goals of such interventions are that the supplements function more as food than as medicine, then more food science and food technology research is necessary. Because some vitamins, such as riboflavin, vitamin C, and folic acid, are perishable, the use of the supplement with other (high temperature) foods and beverages is now seen as critical and merits further study. In the Lima meeting, issues surrounding formulation are described under the heading "delivery issues," which embraces a series of characteristics of a multi-micronutrient supplement. The Lima meeting suggested more latitude and flexibility among the vehicles, considering the medicinal extremes (powders, tablets, liquids), as well as food vehicles (fat-based spreads). Research on the acceptability of any potential product and the bioavailability of its nutrients is necessary. Regarding bioavailability, a working group in Lima identified two potential interactions: nutrient-nutrient and food-nutrient.

The issue of forced creation and ranking of priorities was not a component of the early exercise in Rio de Janeiro, but it was a specific mandate of working group #4 at the Lima meeting. We now know that we cannot really talk about research that we would *like to see conducted* in any academic or theoretical wish list. Rather, we are forced to project choices among various options. The impetus for prioritizing research clearly gathered force over the 2-year interim between the Rio and Lima workshops. One possible explanation is the worldwide economic recession that occurred between 1999 and 2001. The attendees in 2001 were undoubtedly conscious of budgetary constraints in their own lives and work. The factor of actually having the IRIS I study to examine, however, may have been another stimulus toward a mandate to set priorities. Please see pages S58–S61 in this supplement for a working group report by the rapporteurs of breakout section #4 on research [45] for a narrative on how the participants reacted to the matrix in our table 2 and established priorities deemed more or less urgent for immediate action. The presentation of the preliminary findings of IRIS I in Lima provided actual experience to analyze, and in analyzing it, we were guided to weaknesses, deficiencies, and unexpected consequences, and began to build a priority hierarchy suited to address the gaps.

Capacity building for research

The inherent distribution of interests in the issues of micronutrient deficiencies and their partisans has implications for an additional issue: that of capacity building. Inherently, micronutrient deficiencies are more commonly seen in low-income populations in developing countries. This is the region where the benefits are to be realized and where human research must be performed. Public health officials of affected areas should be those responsible for the collective good, and be agents to mobilize resources to improve the micronutrient situation for the populace. They would call for—and call on—the applied research and technology needed to resolve the problems. Various industries can contribute by producing isolated nutrients, preparing supplementation vehicles or food fortificants, and/or processing foods and foodlets. Finally, academic institutions for research (universities, medical schools, institutes) have roles in the diagnostic, surveillance, monitoring, pharmaceutical, and food technology studies.

The poverty and deprivation that would make a region vulnerable to micronutrient deficiency would

also limit the professional and infrastructural development of local health authorities, private industries, and academic institutions. For these reasons, the somewhat 'privileged' consortium of entities involved in the Rio and Lima workshops has a role internationally in framing the 'generic' approaches to solving micronutrient deficiency. It also has the opportunity—and perhaps the responsibility—to advocate for capacity building at the local level to incorporate efforts that will leave the public health, commercial industry, and academic sectors strengthened as a consequence of participating in creating and evaluating interventions against micronutrient malnutrition.

Modern information technology can provide a platform, as well. Websites can contain a plethora of information, including the fundamentals and principles of action, the experiences and lessons learned from activities, and even online "chat rooms" for discussion and information sharing. Websites are generally low-cost, but it is crucial to make sure the information is available in several different languages. More costly, but possibly equally cost-effective, would be to organize local workshops in vulnerable areas to identify and mobilize, then orient and mentor, the appropriate individuals and entities in the health, academic, and business communities. The academic institutions and industries represented in Lima, and the histories of individual workshop attendees, constitute a rich tradition of training professionals competent in micronutrient investigation.

Agencies such as the United Nations University, the International Atomic Energy Agency, UNICEF, etc., can provide mechanisms within their assistance policies to assure that the capacity for designing and conducting high-quality and useful research is imparted to professionals in the countries in which such investigation is most relevant.

Future research directions

Clearly, safety issues must be a top priority of researchers, as well as donors. Faith in the notion so strongly expressed at the workshop in Rio, that "one RDA of a nutrient must be safe," must be questioned. Qualitative differences between one RDA in foods and the same amount in chemical form can exist. This can be mediated by nutrient-nutrient interactions or effects in populations adapted to chronically low intakes. Unless safety is considered, the appropriate indicators may not be measured and adverse effects may be missed. Ethical issues must be carefully weight in any future studies, particularly those involving children.

For studies of bioavailability, radioisotopes are convenient and precise, but they may also represent exposure to ionizing radiation, as well as an environmental hazard. The use of stable (non-radioactive) isotope technology in field studies for both vitamins [46, 47] and minerals [48, 49] has emerged and been perfected, allowing for studies of low invasiveness and no biohazards for both bioavailability and nutrition status monitoring.

Finally, we anticipate a paradigm shift with regard to nutrition research in developing countries [50]—a shift away from interventions only to protect against micronutrient deficiency and toward those that also include longer-term health promotion. Studies suggest that those who took selenium supplements had lower rates of some cancers [51] and higher intakes of antioxidants preventing cataracts or macular degeneration [52, 53]. To become prudent public health policy, any and all modifications of multi-micronutrient dosing must continue to be rigorously assessed to assure that they are safe, efficacious, effective, and efficient (cost-effective), and have the appropriate biologic availability of the nutrients offered.

References

1. Cox HG. The secular city: secularization and urbanization in theological perspective. New York: Simon & Schuster, 1965.
2. Berg A. Sliding toward nutrition malpractice: time to reconsider and redeploy. Annu Rev Nutr 1993;13:1–15.
3. Berg A. Sliding toward nutrition malpractice: time to reconsider and redeploy. Am J Clin Nutr 1993;57:3–7.
4. Jonsson U. The global embarrassment of malnutrition and the role of nutrition engineers (letter). Am J Clin Nutr 1993;58:579–80.
5. Scrimshaw NS. Shattuck Lecture: strengths and weaknesses of the committee approach. An analysis of past and present recommended dietary allowances for protein in health and disease. N Engl J Med 1976;294: 136–42, 198–203.
6. Payne PR. Safe protein–calorie ratios in diets: the relative importance of protein and energy intake as causal factors in malnutrition. Am J Clin Nutr 1975;28:281–6.
7. Sommer A, Tarwotjo I, Djunaedi E, West KP Jr, Loeden AA, Tilden R, Mele L. The Aceh Study Group: impact of vitamin A supplementation on childhood mortality. A randomised controlled community trial. Lancet 1986;1: 1169–73.
8. Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. Lancet 1983;2:585–8.
9. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics 2000;105:E51.
10. Hetzel BS, Dunn JT, Stanbury JB. The prevention and control of iodine deficiency disorders. Amsterdam: Elsevier Science Publishers, 1987.
11. Trowbridge FL, Harris SS, Cook J, Dunn JT, Florentino RF, Kodyat BA, Mannar MG, Reddy V, Tontisirin K, Underwood BA, Yip R. Coordinated strategies for

controlling micronutrient malnutrition: a technical workshop. J Nutr 1993;123:775–87.
12. Maberly GF, Trowbridge FL, Yip R, Sullivan KM, West CE. Programs against micronutrient malnutrition: ending hidden hunger. Annu Rev Public Health 1994;15: 277–301.
13. Scrimshaw NS. Consequences of hidden hunger for individuals and societies. Food Nutr Bull 1993/94:15: 3–24.
14. West KP Jr, Howard GR, Sommer A. Vitamin A and infection: public health implications. Annu Rev Nutr 1989;9:63–86.
15. Arroyave G. The program of fortification of sugar with vitamin A in Guatemala: some factors bearing on its implementation and maintenance. In: Scrimshaw NS, Wallerstein MB, eds. Nutrition policy implementation: issues and experience. Cambridge, Mass.: MIT Press, 1982;75–88.
16. Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D. Vitamin A–fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. Am J Clin Nutr 1988;48:1271–6.
17. Venkatesh-Mannar MG. Control of iodine deficiency disorders by iodination of salt: strategy for developing countries. In: Hetzel BS, Dunn JT, Stanbury JB, eds. The prevention and control of iodine deficiency disorders. Amsterdam: Elsevier, 1987;111–26.
18. Benmiloud M, Chaouki ML, Gutekunst R, Teichert HM, Wood WG, Dunn JT. Oral iodized oil for correcting iodine deficiency: optimal dosing and outcome indicator selection. J Clin Endocrinol Metab 1994;79:20–4.
19. Untoro J, Schultink W, Gross R, West CE, Hautvast JGAJ. Efficacy of different types of iodised oil. Lancet 1998;351:752–3.
20. Eaton SB, Konner M. Paleolithic nutrition: a consideration of its nature and current implications. N Engl J Med 1985;312:283–9.
21. Cordain L. Cereal grains: humanity's double-edged sword. In: Simopolous A, ed. Evolutionary aspects of nutrition and health: diet, exercise, genetics and chronic disease. Basel, Switzerland: S Karger AG, 1999;19–73.
22. Darnton-Hill I, Coyne ET. Feast and famine: socioeconomic disparities in global nutrition and health. Public Health Nutr 1998;1:23–31.
23. Solomons NW, Keusch GT. Childhood illness: childhood illnesses, vaccinations and nutritional status. In: Gershwin ME, German JB, Keen CL, eds. Nutrition and immunology: principles and practice. Totowa: Humana Press, 2000;181–94.
24. Brown KH, Wuehler S, Peerson JM. The importance of zinc in human nutrition and estimation of the global prevalence of zinc deficiency. Food Nutr Bull 2001;22: 113–25.
25. Botto LD, Moore CA, Khoury MJ, Erickson E. Neural-tube defects. N Engl J Med 1999;341:1509–19.
26. Reilly C. Selenium in health and disease. London: Blackie Academic & Professional, 1996.
27. Thu BD, Schultink JW, Dillon D, Gross R, Leswara ND, Khoi HH. Effect of daily and weekly micronutrient supplementation on micronutrient deficiencies and growth in young Vietnamese children. Am J Clin Nutr 1999;69: 80–6.
28. Solomons NW, Ruz M, Gibson RS. Single-nutrient interventions with zinc (letter). Am J Clin Nutr 1999; 70:111–3.
29. Huffman S, Baker J, Shumann J, Sehner E. The case for promoting multiple vitamin and mineral supplements for women of reproductive age in developing countries. Food Nutr Bull 1999;20:379–394.
30. Beckett GJ, Beddows SE, Morrice PC, Nicol F, Arthur JR. Inhibition of hepatic deiodination of thyroxine caused by selenium deficiency in rats. Biochem J 1987;248: 443–7.
31. Thilly CH, Swennen B, Bourdoux P, Ntambue K, Moreno-Reyes R, Gillies J, Vanderpas JB. The epidemiology of iodine-deficiency disorders in relation to goitrogenic factors and thyroid-stimulating-hormone regulation. Am J Clin Nutr 1993;57(suppl):267S–70S.
32. Solomons NW. Biological, ecological and social origins of trace element deficiencies in developing countries. In: Wahlqvist ML, Truswell AS, Smith R, Nestel PJ, eds. Nutrition in a sustainable environment. Proceedings of the 15th International Congress on Nutrition. London: Smith-Gordon, 1994;299–302.
33. Tang AM, Graham NMH, Kirby AJ, McCall LD, Willett WC, Saah AJ. Dietary micronutrient intake and risk of progression to acquired immunodeficiency syndrome (AIDS) in human immunodeficiency virus type 1 (HIV-1)-infected homosexual men. Am J Epidemiol 1993;138:937–51.
34. Idjradinata P, Watkins WE, Pollitt E. Adverse effects of iron supplementation on weight gain of iron-replete young children. Lancet 1994;343:1252–4.
35. Weinberg GA, Boelaert JR, Weinberg ED. Iron and HIV infection. In: Friis H, ed. Micronutrients and HIV infection. Boca Raton, Fla: CRC Press, 2001;135–57.
36. Cooper DA, Eldridge AL, Peters JC. Dietary carotenoids and lung cancer: a review of recent research. Nutr Rev 1999;57:133–45.
37. Solomons NW, Allen LH. The functional assessment of nutritional status: principles, practice and potential. Nutr Rev 1983;41:33–50.
38. Solomons NW. Functional status: functional assessment of nutritional status. In: Sadler M, Strain JJ, Caballero B, eds. Encyclopedia of food science, food technology and nutrition. London: Academic Press, Ltd, 1993; 3295–301.
39. Craft NE, Haitema T, Brindle LK, Yamini S, Humphrey JH, West KP Jr. Retinol analysis in dried blood spots by HPLC. J Nutr 2000;130:882–5.
40. Craft NE, Bulux J, Valdez C, Li Y, Solomons NW. Retinol concentrations in capillary dried blood spots from healthy volunteers: method validation. Am J Clin Nutr 2000;72:450–4.
41. Ahluwalia N, Lönnerdal B, Lorenz SG, Allen LH. Spot ferritin assay for serum samples dried on filter paper. Am J Clin Nutr 1998;67:88–92.
42. Solomons NW. Competitive interaction of iron and zinc in the diet: consequences for human nutrition. J Nutr 1986;116:927–35.
43. Solomons NW. Methods for the measurement of nutrition impact and adaptation of laboratory methods into field settings to enhance and support community-based nutrition research. Nutr Rev 2002;60 (Suppl):S126–31.
44. Gross R, ed. Micronutrient supplementation throughout the life cycle: report of a workshop held by the

Ministry of Health, Brazil, and UNICEF. New York: UNICEF, 2001.
45. Berger J, Solomons NW (Rapporteurs). Report of the research needs working group. In: Gross R, Dwivedi A, Scrimshaw N, eds. International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle, Lima, Peru, May 30–June 1, 2001. Food Nutr Bull 2002;23:313–6.
46. Ribaya-Mercado JD, Mazariegos M, Tang G, Romero-Abal ME, Mena I, Solomons NW, Russell RM. Assessment of total body stores of vitamin A in Guatemalan elderly by the dueterated-retinol-dilution method. Am J Clin Nutr 1999;69:278–84.
47. Tang G, Qin J, Hu S, et al. Protection of vitamin A status in Chinese children by a dietary intervention with vegetables. Food Nutr Bull 2000;21:161–4.
48. Hambidge KM, Krebs NF, Miller L. Evaluation of zinc metabolism with use of stable-isotope techniques: implications for the assessment of zinc status. Am J Clin Nutr 1998;68(Suppl 2):410S–13S.
49. Solomons NW, Janghorbani M, Ting BTG, Steinke FH, Christensen M, Bijlani R, Istfan N, Young VR. Bioavailability of zinc from a diet based on soyprotein: application in young men of the stable isotope tracer, 70ZN. J Nutr 1982;112:1809–21.
50. Popkin BM. The nutrition transition and obesity in the developing world. J Nutr 2001;131:871S–73S.
51. Sunde RA. Selenium (Chapter 33). In: Bowman BA, Russell RM, eds. Present knowledge in nutrition, 8th ed. Washington, DC: ILSI Press, 2001;352–65.
52. Taylor A. Nutritional influences on risk for cataract. Int Ophthalmol Clin 2000;40:17–49.
53. Mayne ST. Antioxidant nutrients and chronic disease: use of biomarkers of exposure and oxidative stress status in epidemiologic research. J Nutr 2003;133 (Suppl 3): 933S–40S.

International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle, Lima, Peru, May 30–June 1, 2001

Reprinted from* Food and Nutrition Bulletin, *Vol. 23, No. 3, 2002

Rainer Gross, Archana Dwivedi, and Nevin Scrimshaw, editors

Abstract

Thirty-one representatives from international organizations, nongovernmental organizations, government agencies, universities, and the private sector participated in a three-day workshop in Lima, Peru, organized by the Universidad Nacional Agraria La Molina and supported by the Ministry of Health Peru, UNICEF, and the World Health Organization. The objective of the workshop was to develop a protocol for a comprehensive micronutrient supplementation program for populations in developing countries that suffer from deficiencies of several micronutrients. The workshop consisted of two components: presentation of preliminary results of the multicenter study on infant supplementation and recommendations on the policy and community, monitoring and impact evaluation, and research aspects of supplementation programs. This paper provides the summary reports of the second component.

Key words: micronutrients, deficiency, life cycle, infants, supplementation

Background

A series of workshops were held in the past two years to foster multi-micronutrient supplementation and fortification. Based on the ideas discussed in the workshops, several multi-micronutrient supplementation trials have been conducted, which provide information on efficacy in different age groups. It is time to reflect on the results of these trials and explore the lessons learned from these experiences to develop a comprehensive multi-micronutrient supplementation program addressing deficiencies in different age groups based on the life-cycle approach.

Rainer Gross, formerly with the GTZ Programa Postgrado Nutricion Publica at the Universidad Nacional Agraria La Molina in Lima Peru, is now Chief, Nutrition Section, Programme Division at UNICEF, New York, USA. Archana Dwivedi is Project Officer, Nutrition Section, Programme Division, UNICEF, New York. Nevin Scrimshaw is Senior Advisor, United Nations University Food and Nutrition Program (UNU), Boston, Mass., USA.

Objective

The objective of this technical workshop was to discuss the elements of a comprehensive micronutrient supplementation program for populations in developing countries that simultaneously suffer from the deficiency of several micronutrients. In particular, its purpose was to:

» present, analyze, and discuss the results of the international research on infant supplementation (IRIS) I multicenter study;
» present, analyze, and discuss the studies on the relative bioavailability of the multi-micronutrient supplement used in the IRIS I study;
» define the multi-micronutrient dosing for supplementation of all age groups within the context of the life-cycle approach;
» formulate indicators for monitoring and evaluating multi-micronutrient supplementation programs;
» formulate a protocol for a comprehensive multi-micronutrient supplementation program based on a life-cycle approach to be tested in different settings.
ignore dashed lines above

Program of the workshop

Thirty-one experts from 13 countries of South and North America, Asia, Africa, and Europe, working for international agencies (IAEA, UNICEF, GTZ, and USAID), governmental organizations (Peru, South Africa, and Vietnam), universities (Brazil, Germany, Peru, UK, and USA), nongovernmental organizations (AJCN, USA; CeSSIAM, Guatemala; Instituto de Investigación Nutricional, Peru; MI, Canada; and Nutrinet, France), and five specialists from the private

sector (Chile, Peru, and Switzerland) came together from May 30 to June 1, 2001, in Lima, Peru, to discuss recommendations for micronutrient supplementation. The workshop was organized by the Universidad Nacional Agraria La Molina and supported by the Ministry of Health of Peru, UNICEF, and the World Health Organization (WHO). The workshop consisted of two components. In the first, preliminary results of the multicenter study IRIS I were presented and discussed. In the second part, three working groups were formed to discuss recommendations for future studies and interventions in the field of multi-micronutrient supplementation. Group 1 focused on community and policy aspects, group 2 discussed monitoring and impact evaluation issues, and group 3 deliberated over research needs. The results of each working group were presented and discussed. The rapporteurs considered additional comments from the plenary session in their final version of the report. The results of these three working groups follow.

Report of the Community and Policy Working Group

Rapporteurs: Erick Boy and Nevin Scrimshaw

Introduction

» In almost all developing countries, significant problems of multiple micronutrient deficiencies occur in children 6 to 24 months of age that urgently need attention. By this age the iron stores of the infant are depleted, and the breastmilk can no longer supply sufficient iron.
» Multiple fortification of cereal flours and other foods benefits older children and adults but does not sufficiently benefit this age group. The failure to provide additional iron at this critical age can have permanent adverse consequences for the cognitive development and education of the child.
» The child is growing rapidly at this age and needs a balanced complement of micronutrients not provided by the complementary feeding practices of lower-income mothers in most developing countries.
» Unless the mothers can afford fortified complementary foods, supplementation is the only feasible approach.
» Activities focused on the mothers to improve the nutrition and health status of children aged 6 to 24 months should not be neglected. Universal fortification of cereals with iron and selected other micronutrients will ensure a certain minimum level of iron status of the mother, but this should be complemented by supplementation of women of childbearing age to ensure that they enter pregnancy adequately nourished, and supplementation should be continued during pregnancy and lactation. In particular, adequate iron status of the mother is essential to ensure that the iron stores of the infant are sufficient for months, with exclusive breastfeeding as long as appropriate.
» For low-birthweight infants, iron supplementation may be required as early as two to three months.
» Other health interventions that benefit both the mother and the young child include spacing and limitation of pregnancies, environmental sanitation and hygiene to reduce enteric diseases, and treatment of malaria where it is endemic. Delayed ligation of the cord can significantly improve the iron stores of the infant. There are also many studies indicating that improving the general education and status of women in developing countries is an important measure benefiting the nutrition and health of all members of their families
» Successful implementation of such policies depends on effective monitoring and evaluation.
» While the deficiency of iron in this age group in developing counties is almost universal, and deficiencies of folate and zinc are recognized concerns, the young child should receive a balanced addition of micronutrients to his or her diet, because single nutrient deficiencies are rare. Moreover, as noted in the first IRIS workshop held in Rio de Janeiro in 1999, and still equally true, "Since operational strategies and distribution systems can be similar for each micronutrient, it is cost-effective to avoid duplication." Moreover, the incremental costs of additional nutrients are very small. Therefore, the workshop recommends the IRIS concept of multi-micronutrient intervention for children 6 to 24 months old.
» Since single deficiencies are rare, such a supplement should supply the most essential multiple micronutrients. Many different types of supplements can be used, ranging from liquids to powders to tablets and spreads. This is the IRIS concept.
» Preliminary findings from the IRIS I project have demonstrated in four different countries and cultural contexts the feasibility and acceptability of a

Erick Boy is affiliated with the Micronutrient Initiative in Ottawa, Canada. Nevin Scrimshaw is Senior Advisor, United Nations University Food and Nutrition Program (UNU), Boston, Mass., USA.

friable tablet that can either be crushed and added to any food given to the child or broken into pieces and fed directly.
» It is not only a moral obligation of governments to address this problem, but also a legal obligation under the convention of "Rights of the Child," to which almost all countries subscribe. Moreover, the short- and long-term economic benefits of supplementation of this age group far outweigh the costs.

Need for situation analysis

» Determination that iron and a number of other nutrients are significant nutrition problems in a population.
» Agreement on the levels of each micronutrient in the supplement.
» How best to provide education, information, and communication to policy makers, implementers, and families as to the reasons for the urgency of interventions to improve the nutrition and health of this specific age group. It is essential that mechanisms for doing so be communicated and that the need for the recommended behavioral changes be recognized.
» How best to deliver a supplement to children 6 to 24 months old, and how to present it to the mother and child. It must be accessible, affordable, attractive, and safe. Hence, suitable packaging and instruction for its use are essential.

Policy problems and issues

» Choice of number and frequency of supplementations needs to be established.
» Lack of definition of the problem and priority for this neglected age group. Need to define and advocate for this target group.
» Better information on the timing and nature of complementary feeding is required.
» Need for flexibility of approach in the method of providing micronutrients to this age group.
» Need to better define the relation between the health and nutrition of the mother during pregnancy and lactation and the nutrition of the infant.
» Inadequate data for this age group because it is usually aggregated with that of older age groups.
» Need to ensure an adequate supply of whatever supplement is introduced and promoted and its uninterrupted delivery to distribution centers.

Implementation mechanisms

There is a great need for an institutional focus of responsibility. There needs to be an institution or organization designated as responsible for the implementation of a program for supplementation of children 6 to 24 months of age. This will vary among countries but is likely to be most effective when it is multisectoral and not limited to the health sector. Regardless of the administrative structure, it must have highly motivated leadership and political support. It must be capable of enlisting the support of all sectors involved, including local political authorities and communities.

It is essential that the community be enlisted in support of the program from its inception and convinced of its importance for the health and welfare of their children. The community should be given an opportunity to make the decision to implement the program and to play an active role in its promotion to families and in monitoring compliance. The support of community civil and religious organizations can sometimes be crucial. In some countries, nongovernmental organizations can play an important supporting role. In general, intervention programs of this type will fail unless they can enlist community support nationwide.

For any policy to be adopted by a government it must be presented at an appropriate time in the planning cycle.

Conclusions and recommendations

The studies in all four sites indicate that giving a multinutrient supplement weekly that provides two times the recommended daily allowance (RDA) results in an improvement in hemoglobin and anemia as compared with the placebo group. Although the response to daily supplementation with one RDA appeared to be greater in three of the four sites, daily supplementation costs more, and there is evidence from some countries that daily supplements are more difficult to distribute and to secure compliance with.

It is also recognized that supervised supplementation may not be fully applicable to the effectiveness of national programs because of cost and compliance. It is essential to determine whether the better hemoglobin response at three of the four sites with daily supplementation justifies the higher costs.

The working group concluded that in most countries, weekly distribution would prove feasible and sustainable for the reduction of iron deficiency. It will be important to assess the effect of the multiple micronutrient supplementation program on the status of other important nutrients measured as outcomes of the IRIS program.

The feasibility of cost recovery from the community or the family needs to be determined. In general, it is desirable to develop a system of cost sharing. Experience in some countries (Thailand, Vietnam, and Bolivia) indicates that this is usually feasible, improves compliance, and makes the program more politically acceptable and sustainable by reducing the cost to the government.

Monitoring and impact evaluation of a multi-micronutrient supplementation program

Rapporteurs: D'Ann Finley, Klaus Schümann, and Denise Hess-Bienz

Monitoring and impact evaluation, as defined in this workshop, occur after the efficacy and effectiveness of the multi-micronutrient supplementation program have been demonstrated and a large-scale intervention program has been implemented. If a preliminary program is being monitored, additional money must be allocated to evaluate whether the program should be scaled up to a full-scale program. In some places, the supply and distribution of supplements will be restricted to the public sector, whereas in others, some or all of this task will occur in the private sector. This workshop, however, was restricted to the public sector. If monitoring systems for other ongoing programs are already in place, these systems should be used, where appropriate, in order to make optimal use of resources and to simplify processes.

Policy review

The task of the monitors is to identify bottlenecks in the program and to flag them, i.e., to provide the information to the person in charge of the operation who can take appropriate action. The first monitoring step is to determine whether there is already a policy in place that will allow the implementation of the program, regardless of whether policies are implemented at a provincial or a national level. On a yearly basis, it is important to determine the extent to which the individuals responsible for implementation of the program are aware of these policies, and whether they understand them. It is also important to determine yearly whether the intervention program has been included in the appropriate budget and whether the necessary resources have been allocated in order to ensure continuing funding by the government. If an agency supports only the initiation of the supplementation program, it is important to determine who will take over support and monitoring of the program after the agency leaves.

Supply and distribution of supplements

Coverage is the percentage of the target group that receives the materials, and compliance is the percentage of individuals who consume the product in the specified amounts. Adequate coverage is the final consequence of a well-functioning supply and distribution system and should be monitored. Compliance can be checked by surveys on representative subgroups of the target group. The ordering of the product needs to be monitored. Key questions include: Is there a plan for ordering and requisitioning the supply according to need? Is the supply central or provincial? How much needs to be ordered? Was the amount ordered actually delivered?

The stock must be controlled for quantity and quality, whether it is kept on a central or a provincial level. To certify the content and quality of the micronutrients in the product is the manufacturer's task. The storage conditions should be monitored to identify any potential detrimental effects on the product. The supply itself has to be monitored for expiration dates, and any outdated stock has to be destroyed. Finally, the transportation of the supply and its dispensation to the place of use, for example, a health center, has to be monitored. Storage time and conditions at the place of use should also be monitored.

Each program needs a monitoring system, but this system needs to be supervised as well. The supervisor must check whether requisition forms are available where needed and whether they are completed accurately.

Training and education

Each aspect described above for monitoring the distribution of the product also applies to monitoring the training of the people engaged in the distribution of the supplement. This consists of information, education, and communication (IEC). Important questions in this respect are: Is there an adequate budget? Are the training materials available? Are they distributed? The IMCI (Integrated Management of Childhood Illness) system is an example of a system that monitors the delivery of services and the performance of staff in immunization programs.

The target population, including the caregiver, should receive information and education on the benefits of the micronutrient supplementation program, e.g., by use of social marketing techniques. The goal is to create a "push and pull" situation. A demand for the supplement from a well-educated population is an important part of the success of an intervention program and represents the "pull" part of the distribution

D'Ann Finley is affiliated with the University of California in Davis, California, USA and is the co-editor of the American Journal of Clinical Nutrition. Klaus Schümann is a Professor at the University of Munich, in Munich, Germany. Denise Hess-Bienz is affiliated with Roche Vitamins, Ltd. in Basel, Switzerland.

process; availability and adequate supply represent the "push" part, since success is finally dependent on behavioral changes in the population.

Surveying changes in behavior and biochemical indicators

Valuable information on the general nutritional situation in a locality can be obtained from a variety of sources, such as the number of cases of severe anemia admitted to the hospital or the change in prevalence of overt clinical signs and symptoms. However, it seems very difficult, if not impossible, to disentangle the impacts of different programs that are simultaneously active at a given site or within a given population. The same holds true for the impact of events outside of these programs, such as droughts, changes in the economic situation, or political events. Therefore, trying to assign a specific change in behavior or in a biochemical indicator to a particular program is fraught with hazards.

In order to be able to monitor change, either in behavior or in biochemical indices, it is important to have baseline data available. Ideally, for a compliance survey the individuals initiating the program would do a baseline survey before the program started and a follow-up survey after it has been in effect for a long enough time that one would expect to see results. However, the costs and availability of facilities to do a specific baseline survey for a program are important constraints. Therefore, any available source of data should be evaluated for its usefulness as a baseline.

Usually baseline surveys have been done to provide evidence that the program is needed and to justify its initiation. Demographic and Health Surveys (DHS), Expanded Program of Immunization (EPI) surveys, and National Nutrition Surveys (NNS) are done in many countries on a routine basis. If possible, the individuals initiating the program should coordinate with one or more of these surveys in order to maximize the amount of information obtained. Therefore, a primary question is whether these survey data are available and current. If they are, the next question is whether they provide the necessary information to be used as baseline data for the program.

The ideal baseline survey would include three basic elements: anthropometry, a blood sample for analysis, and a questionnaire. Anthropometric data would be collected by standardized methods. The blood sample would be analyzed for variables of interest, such as hemoglobin, retinol, red blood cell count, zinc, ferritin, and markers of inflammation. The questionnaire should include questions on personal data, morbidity, and diet, and specifically for a micronutrient supplementation program, knowledge about micronutrient supplementation.

The follow-up survey would include the same three elements, and the questionnaire would be expanded to include questions on compliance and behavioral change. These questions would include the following: Did the mother or caretaker receive the supplement? Did she give it to the child? Did the child take it? What effect does the mother think the supplement will have on the child? Why does she think she should give it to the child? The questionnaire should also include questions about potential side effects of the program and the interaction of this program with other programs.

Conclusions

An important task of the monitoring and impact evaluation will be to communicate its results. Was the intervention program a success or a failure? What were the critical issues, particularly the problems encountered during the program with the policies, supply chain, compliance, and education? Only the effective communication of these issues to the appropriate audience will help future programs to be successful.

Report of the Research Needs Working Group

Rapporteurs: Jacques Berger and Noel W. Solomons

Introduction and approach to the task

The topic and context of the work of the Research Needs Working Group was the need for investigation of more effective impacts of multiple micronutrient interventions. The background for the discussion was the overview, technical information, and data presented in the International Workshop on Multi-Micronutrient Deficiency Control in the Life Cycle. Notably, the results in the multicentric IRIS (International Research on Infant Supplementation) were the immediate concrete context for discussion, but the group interpreted the mandate in a somewhat broader dimension.

At the applied investigation level, a number of descriptive terms (efficacy, safety, effectiveness, and efficiency) are commonly used. The working group

Jacques Berger is a affiliated with the Institut de Recherche Pour le Développement in Montpellier Cedex, France. Noel W. Solomons is affiliated with the Center for Studies of Sensory Impairment, Aging and Metabolism (CeSSIAM) in Guatemala City, Guatemala.

began its deliberations by coming to a consensus on key working definitions. *Efficacy and safety:* Biological effect under controlled experimental conditions. *Effectiveness:* Effect in real-life situations. *Efficiency:* Ratio between results achieved and resources consumed.

With respect to the design for implementation of multi-micronutrient intervention programs, these critical parameters must be addressed both before and during the implementation and monitoring process.

As a second step, the working group set out in matrix format a potential agenda for discussion and "brainstorming" during the course of its deliberation. The notion was to have a focus on the consensus issues that the group's members as a whole considered relevant for discussion in order not to focus on a limited number of issues of importance for the research agenda. This set of principal terms and component terms is laid out in table 1.

Setting a research agenda

From definitions and brainstorming, the working group discussed the topics identified on the agenda. For each topic, we present the research questions identified and a justification for addressing them with continued investigation, as well as reflections on the topic by the group.

TABLE 1. "Brainstorming" agenda/matrix

Efficacy/safety
Dosing
Low birthweight
Pregnancy
Functional vs. biochemical outcomes
Disease issues
Bioavailability
Nutrient interaction
Food/carrier
Delivery issues
Vehicles
Fat
Powder vs. tablet vs. liquid
Bioavailability
Acceptability
Behavioral issues
Compliance
Cultural perception
Dosing schedule
Communication
Cost-benefit
Relation to efficiency
Affordability issues
Assessment
Magnitude and severity of different micronutrient deficiencies
Cutoff in different age groups
Need for new assessment methods
Intervention: biochemical outcomes
Intervention: functional outcomes/disease issues not attributable to single micronutrient: growth, morbidity, stress indicators: efficacy/safety

Dosing issues

The question identified as requiring research within this area is: Should the doses of micronutrients be linked to multiples of the RDA?

The justification for revisiting the use of RDA multiples for creating dosages in supplements has several facets. Some nutrients (e.g., calcium, zinc, and iron) are poorly tolerated in high multiples of the RDA, and even doses of two or three times the RDA may be difficult to swallow or tolerate in a supplement. Moreover, other nutrients, such as thiamin and vitamin C, are so poorly stored that high multiples will not be retained beyond the day of supplementation. Finally, even in developing countries, the background diet or setting can provide such abundant supplies of some nutrients, e.g., vitamin E from whole grains or oils and vitamin D from tropical sunshine, that no supplementation is needed.

The RDA levels blended across the nutrients represent a common balance among the different nutrients, reflecting the pattern in an appropriately balanced diet. A minority dissenting admonition was that high-multiple RDA formulations can be dangerous, especially adult RDAs when they fall into the hands and mouths of young children and are consumed accidentally.

Delivery issues

The group identified three levels of delivery issues:

» Food format. Is the supplement presented in a medicinal form, i.e., as a powder, elixir, pill, or tablet? Or is the supplement presented as a beverage or in a food, such as a spread?
» Bioavailability issues. How absorbable are the nutrients from the preparation? How utilizable are they after uptake?
» Miscellaneous issues. Does the preparation contain fat? Does it have animal-based additives that might be taboo for consumption by members of certain religious groups?

The questions identified as requiring research within this area are:

» What are the effects, if any, of nutrient-nutrient interactions on safety of the formulation?
» What are the effects, if any, of nutrient-nutrient interactions on efficacy of the supplement?
» What are the effects, if any, of nutrient-food interactions on safety of the formulation?
» What are the effects, if any, of nutrient-food interactions on efficacy of the supplement?

The justification for addressing these questions derives from the well-known interactions such as those between zinc and iron, calcium and iron, calcium and zinc, food phytates and metals, and food fats

and lipid-soluble nutrients. The efficiency of nutrient uptake may determine the outcome of supplementation for improved nutrition and adversely excess exposure. Additional comments included the notation that some, but not all, micronutrients have bioavailability issues. Some are absorbed with a fixed efficiency by the intestine without any factors known to enhance or inhibit uptake.

Target groups for intervention

The questions identified as requiring research within this area are:

» What are the appropriate target groups for interventions?
» How long during the life span should different interventions be sustained?

The justification for these recommendations can be summed up in terms of the existence of vulnerable groups with lower possibilities of meeting their RDAs through diet and having micronutrient-deficiency burdens. More research is needed to focus appropriately on subgroups within age-group categories that might have different needs. For instance, a formulation for the average toddler may not be sufficient for those who are of low birthweight. Formulations for pregnancy may not meet the needs for adolescent pregnancies.

Additional comments led to a discussion of whether interventions are justified on the basis of a human right to an adequate nutrient intake or are based only on demonstrable capacity to reverse existing micronutrient deficiencies. With respect to targeting, would the recipients be only the poor and vulnerable subpopulations within a society, or all members of a society? If any safety issues concerning excess exposure to one or another micronutrient were detected for a disadvantaged and underprivileged subpopulation, such concerns would surely be magnified for the more affluent members of the same societies.

Assessment of background status

The following question was identified as requiring research within this area:

» What are the pre-existing rates of inadequacy (deficiency) or adequacy in the potentially targeted populations?

The justification for these recommendations, which basically call for a survey of the populations of interest, is the fact that the need to motivate policy authorities to action requires showing them the evidence for the problem and its nature. However, it is impossible to assess the population nutriture for certain micronutrients. Moreover, if the model of a single-RDA dosage is under consideration, certain nutrient deficiencies (e.g., iron, zinc, and vitamin A) may not be efficiently or effectively addressed by supplementation at this level.

Assessment of biological impact issues

The following question was identified as requiring research within this area:

» What are the effects of multiple-micronutrient modules on functional outcomes for young children (growth, development, and disease resistance)?

The justification for these recommendations rests in the debate between evidence from "static" versus "functional" indicators of nutritional status. Sometimes, for policy justification, deficits in functions such as growth, development, or disease resistance are more motivating than evidence such as low biochemical concentrations. For safety, as well, evidence of dysfunction may be more interpretable and compelling than laboratory indices.

Functional outcomes with multinutrient interventions cannot be attributed to any specific nutrient. The nutrients are offered as an integrated package, and the results must be so interpreted. Given the low dose of each nutrient in the intervention, the question arose as to the basis for justifying the program by being able to show increased growth, better development, or higher resistance to infection. On the safety side, do we wait for a "functional" indicator of an adverse effect, e.g., decreased growth, to appear? For safety, monitoring of more sensitive and earlier indicators of adverse effects arises. These could be indices of elevated storage reserves or of oxidative or inflammatory stress.

Behavioral and anthropological (social science) questions

The questions identified as requiring research within this social sciences-related area are:

» What are the constraints to daily, intermittent, or weekly dosing?
» What are the complementary food contexts for feeding micronutrient interventions?
» What are the customs and perceptions of the target population?
» What is the acceptability of various micronutrient supplementation formats?

The justification for these questions is the inherent a priori ignorance about acceptability issues of new practices before the practice has been introduced. The constraints to daily, intermittent, or weekly dosing will differ from country to country. Clearly, schoolchildren and factory and plantation workers are more readily reached. Compliance with any approach, including "foodlets," will depend on local customs, culture, and perceptions.

Some dissenting and nonconsensus statements arose. One member felt that the efficacy of weekly dosing intervals as measured by some outcomes in the IRIS data may be too "weak" to justify this dosing interval for programmatic action. It was recognized that the

dosing schedules could be "top down," i.e., dictated by public health authorities, or "bottom up," in which the behavioral possibilities are identified by the community and the dosage pattern is adapted to the culture. Both approaches have advocates.

Overall priority ranking

At the conclusion of deliberation, the group was polled as to which of the terms of the research agenda matrix in table 1 were to be considered to have the highest priority. Since members rated either one or two terms, a weighted rating of terms is provided in table 2.

Conclusions

There are multiple micronutrient deficiencies in the disadvantaged populations of the world, and a multinutrient solution or solutions are needed. To achieve this goal, the policy and program interventions must be supported by research. The working group, addressing the perceived gaps in our epidemiological, behavioral, and technical understanding and capacity for devising and implementing programs, has formulated a series of research questions. The highest areas for inquiry are efficacy and safety of multiple micronutrient supplements. It is hoped that resources can be mobilized to address the agenda, and that addressing the outlined research will truly facilitate the programmatic solutions.

TABLE 2. Global priority rating for the research agenda in future multi-micronutrient investigation

Item	Chosen priority
Efficacy studies	6
Safety research	3
Magnitude of deficiency	2
Behavioral research	2
Effectiveness research	1
Bioavailability studies	1